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THE HEART IN FUNNEL CHEST.

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FUNNEL chest (pectus excavatum, Trichterbrust) is characterized by a depression of the lower end of the sternum. It was first described by Bauhinus[1] in 1594. It was again mentioned in an anonymous note[2] in 1860, and in March of the same year Woillez[3] described the case of Heinrich Wojaczek, a young Viennese medical student. Thereafter occasional reports on isolated or comparatively small groups of cases appeared, and in 1909 an exhaustive study of the literature was made by Eric Ebstein.[4] Although he collected 97 previously reported cases, his work was essentially a discussion of the various theories of the etiology of trichterbrust and was incomplete from the clinical point of view.

The deformity varies considerably in size and depth—from a very slight depression to one in which the entire sternum is involved. The deformity of Woillez's patient was considerable, measuring 25 cm. in the vertical diameter, 18 cm. transversely and 7 cm. in depth. In his case Woillez estimated the distance between the anterior surface of the spine and posterior surface of sternum at its deepest part to be but 1 cm. Although mild cases of funnel chest are common, the moderate and severe forms are infrequent, but not as uncommon as the meager literature would lead us to

believe. Eichhorst[5] found 6 cases among 14,000 patients and Rosenfeld[6] found 4 cases among 4386 deformities of various types. We have been able to assemble 10 cases of moderate or severe degree (Table 1) in a comparatively short time. Three cases were referred by an orthopedic surgeon, 2 by two medical colleagues and the remaining 5 cases were seen in private practice.*

Most cases of funnel breast are either congenital or acquired in early life; a third class is definitely traumatic in origin. The congenital type has been ascribed to various causes. Eggel[7] believed it due to a nutritional disturbance, causing a softening of the sternum which permits it to be depressed by atmospheric pressure. Langer and Zuckerkandl,[8] and Ribbert,[9] pointed out the possibility of extrauterine pressure as the cause. Von Heuter and Niemeyer[10] considered it a manifestation of fetal rickets. Syphilis was thought to be the etiologic factor by Gaucher.[11] W. Ebstein[12] believed it due to an embryologic defect or arrest of development of the sternum. Flesch[13] ascribed it to an abnormal length of the ribs. The acquired type has been ascribed to rickets,[14] obstruction to respiration because of adenoids and asthma,[15,16,17] faulty posture,[18] mediastinal adhesions.[19] Déjerine[20] has seen it in association with progressive muscular paralysis. While it is not within the province of this paper to discuss the various theories proposed to explain this deformity, it is agreed that the congenital cases are developmental and the changes in position of the heart and other viscera described below have been found in infants at birth.[1,21,22] In most of the acquired cases the deformity which is small and usually noted at an early age[18] increases in size with the growth of the thorax.

Signs and Symptoms. Because the excavation usually involves the region of the precordium, the thought presents itself that serious cardiac disturbance might readily occur. However, among the uncomplicated congenital cases, comparatively few complaints of cardiac symptoms have been noted irrespective of the size of the depression. (Table 1.) Sauerbruch has reported 2 cases having only mild funnel chest deformity associated with cardiac symptoms, but such cases are apparently exceptional. The tremendous deformity of Woillez's case was discovered during routine examination, for the young man, 23 years of age, was in excellent health and had never complained of cardiac or pulmonary symptoms. It is also interesting to note that this same Heinrich Wojaczek exhibited himself before the various European clinics for many years. Our oldest patient, I. C. (Table 1; Fig. 1), was 69 years of age and was symptom-free and had never any serious cardiac or pulmonary disorder, although his deformity measured 10 cm. in transverse diameter, 9½ cm. in vertical diameter and was 5 cm. deep. Judson's[24]

* We wish to express our thanks to Dr. A. M. Rechtman, Dr. J. Q. Griffith, Jr., and Dr. Sloan Stewart for referring the above cases.

TABLE 1.—DATA ON 10 CASES OF FUNNEL CHEST.

No.	Initials.	Sex.	Age years.	Etiology.	Duration.	Depth of depression.	Ext. depth of chest.		Inter. diam. of chest.		Heart diam.		Index.	E.K.G.	Cardiovascular symptoms.	Exercise tolerance.	Complication.
							At deformity.	Above.	Transverse.	A.P.	Transverse.	A.P.					
1	C. Y.	M.	7 mos.	Cong.	7 mos.	1.5 cm.	8.0	9.5	Not meas.	..	Not meas.	..	..	Normal	None		
2	J. C.	M.	9	Cong.	9 yrs.	2.0	9.3	12.2	18.4	6.0	10.0	5.4	5.40	Normal	None	Good	None.
3	M. W.	M.	11	Cong.	10 yrs.	3.0	9.5	12.5	20.0	7.0	10.3	5.5	5.34	Normal	None	Good	None.
4	J. A.	M.	14	Acq.	10 yrs.	3.5	15.5	19.0	19.3	10.5	...	..	..	Normal	None	Good	None.
5	M. W.	M.	17	Acq.	5 yrs.	3.0	13.0	16.0	24.7	7.2	10.5	6.8	6.48	Normal	None	Good	None.
6	W. A.	M.	19	Acq.	9 yrs.	2.0	17.0	19.0	21.6	14.0	13.0	9.8	7.54	*Q–R–S*¹ split	Dyspnea, cyanosis, edema of ankles	Poor	Kyphoscoliosis; pigeon breast.
7	J. C. H.	F.	22	Not	known	Not measured; moderate	...	...	25.1	..	12.0	6.2	5.20	Normal	Severe attacks of precordial pain	Fair	Hist. of rheum. fever and pericarditis at 8 yrs.; moderate scoliosis.
8	W. L.	M.	33	Cong.	33 yrs.	Not measured; extreme	...	...	...	..	...	..	..	Paroxysms of aur. fibril.	Parox. aur. fibril. for 8 yrs.	Good	None.
9	N. W. P.	M.	34	Acq.	22 yrs.	4.0	14.0	18.0	25.0	7.0	12.7	7.9	6.20	Prolonged *P–R* interval	Low blood pressure; weak	Good	Myocardial disease?
10	I. C.	M.	69	Cong.	69 yrs.	5.0	15.0	20.0	26.4	7.8	12.0	7.9	6.60	*Q–R–S* complexes split and widened; left axis deviation	None	Fair	None.

patient, a man, aged 71 years, also was symptom-free. It is difficult to conceive of the heart being so markedly displaced and flattened as in Fig. 2 without showing evidence of cardiac dysfunction, but the slow development in the congenital and most of the acquired cases probably allows for accommodation not only within the chest but also within the heart.

In the vast majority of cases the deformity is noted at birth or in early childhood and is comparatively small. Occurring at a time when the organs have the greatest power of adaptation and long before the growth of the thorax is complete, the narrow anteroposterior diameter of the chest is compensated by an increased growth in breadth of the chest; the heart, mechanically impeded in its growth by the depression, compensates by a comparatively greater increase in its transverse diameter. None of our cases showed an undue twist or kink of the aorta, the slow development probably allowing for compensation.

Rapid formation of the depression, as seen in traumatic cases, does not allow for this accommodation and, according to the literature, symptoms, especially pain and dyspnea, are usually present. Alexander[25] recently reported 2 cases of traumatic funnel breast. Pain and dyspnea, which were prominent symptoms in both cases, were relieved by operation.

It is difficult to evaluate the symptomatic effect of funnel breast upon those cases complicated by a spinal deformity and those associated with organic diseases of the heart. We shall show in a future paper that spinal deformities, especially scoliosis and kyphoscoliosis, exert a profound influence upon the size, shape, position and functional capacity of the heart. The chest is distorted and the lung on the side of the deformity is compressed while the opposite lung shows a compensatory emphysema. Furthermore the chest is fixed and does not allow proper ventilation of the lungs; the chest is often small, for the deformity is usually complete before bodily growth and therefore lags somewhat behind. In some cases the pulmonary artery is found kinked and twisted at postmortem. The above factors all throw an added load upon the right heart. As a result signs and symptoms referable to weakness of the right heart appear early. Our patient (Fig. 3) complained of dyspnea, edema of the legs and was somewhat cyanotic. Although there was a moderate funnel chest, the kyphoscoliosis is compensated for by the depression. Since the heart was not compressed, the funnel chest probably did not play any part in the production of his symptoms.

Another patient, a draftsman, first observed the depression at the age of 12 years and was well until he was 34 years, when he developed weakness and low blood pressure. At preparatory school he was a cross-country runner and played ice hockey, basketball and tennis. During the World War he was in the navy and at no time experienced any symptoms referable to the cardiovascular

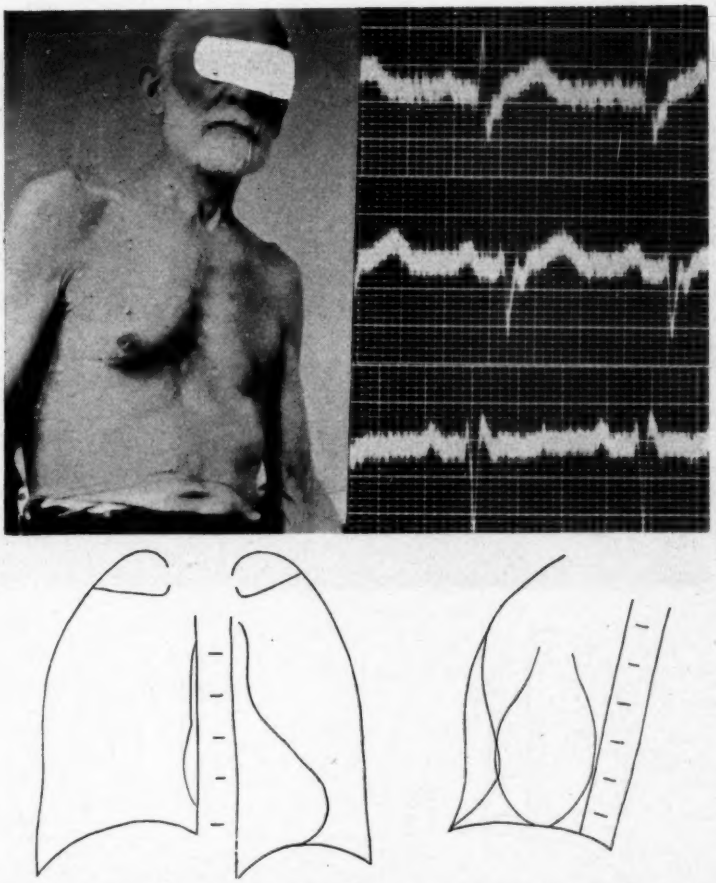

FIG. 1.—Case 10. Congenital funnel chest in man, aged 69 years. In lateral view note the clear space in front of heart, the anterior border of which is formed by the chest wall, the posterior by the depressed sternum. The heart is displaced to the left and slightly upward and because of the asymmetry of the depression, its anterior border is seen in front of the shadow of the sternum.

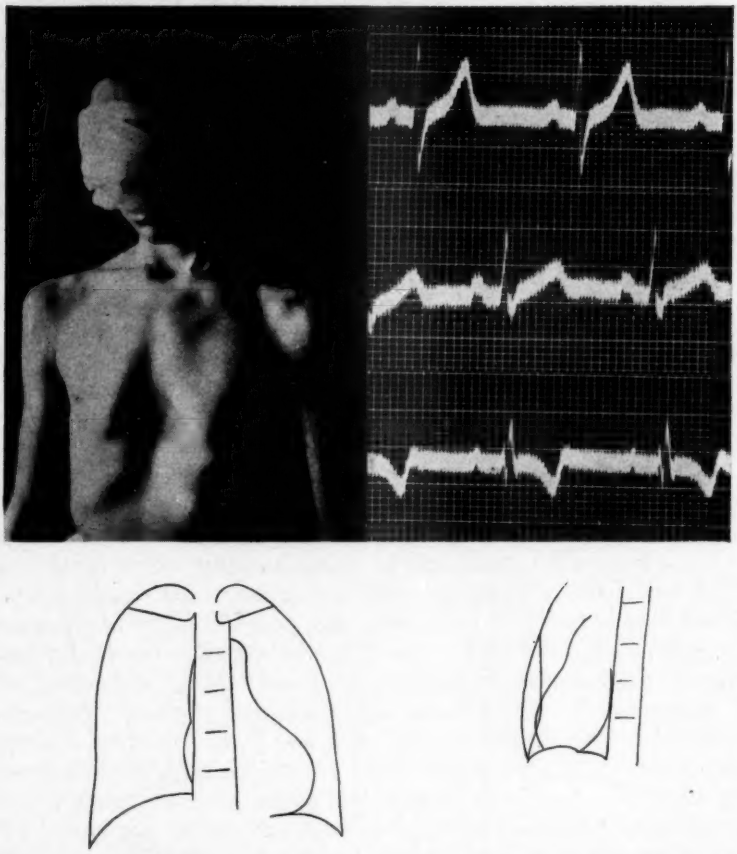

FIG. 2.—Case 3. Congenital funnel chest in boy, aged 11 years. The heart is markedly flattened in the anteroposterior diameter and is displaced to the left and slightly upward.

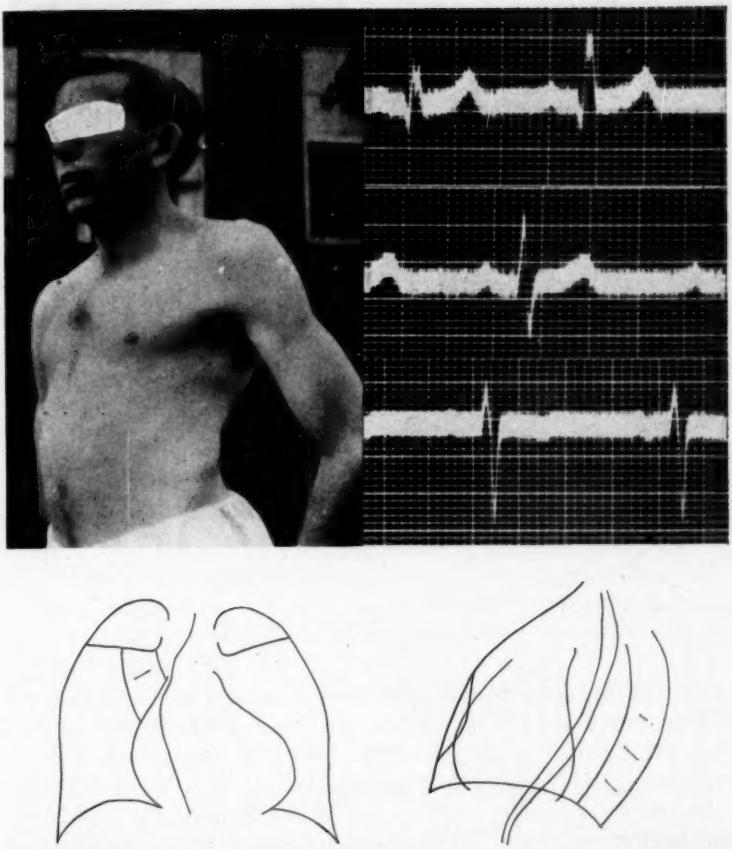

FIG. 3.—Case 6. Acquired funnel chest in young man, aged 19 years, complicated by a kyphoscoliosis and pigeon breast. The heart is not displaced or flattened. Note the scoliotic spine to the right of the heart. The esophagus is seen behind the heart.

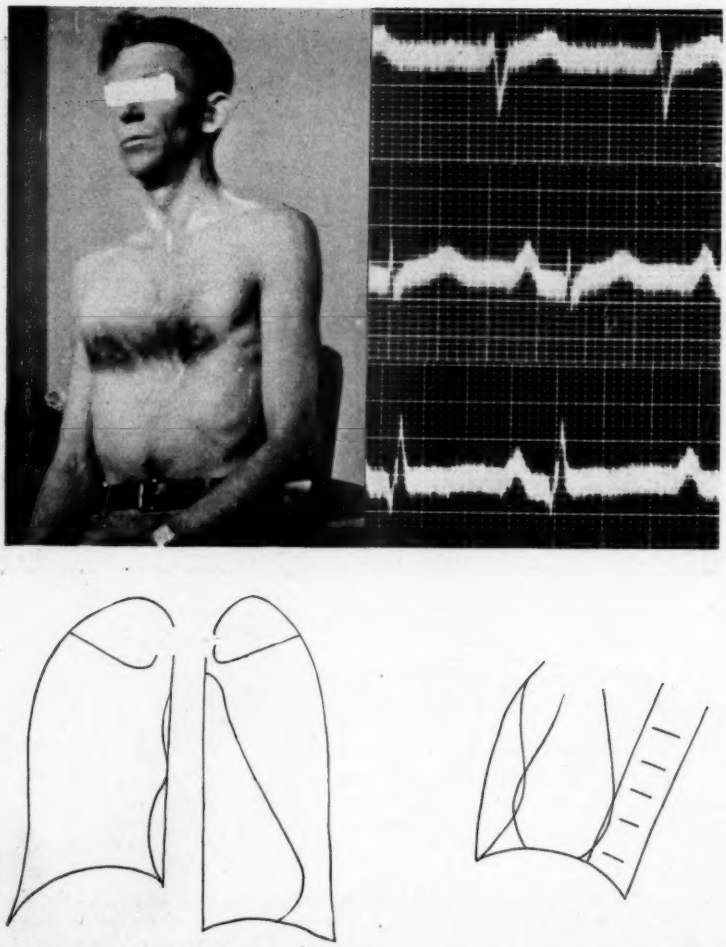

FIG. 4.—Case 9. Acquired funnel chest in man, aged 34 years. The depression is primarily left side. Note the "mitralization" of the heart, probably the result of rotation by the left-sided depression.

system. Although it is impossible to state with certainty what effect his funnel depression had upon his present condition, it is improbable that a condition which apparently did not affect his cardiovascular system during his strenuous athletic career would affect it seriously during a period of comparative inactivity. The depression in this case has the uncommon feature of being primarily left-sided. Fluoroscopically, the heart appeared rotated to the right by the left-sided depression, and this probably accounts for the "mitralization" (Fig. 4) and the right axis deviation observed in the electrocardiogram. (Fig. 4.)

Sauerbruch[23] reported a case of paroxysmal fibrillation in an uncomplicated funnel chest which cleared up after operation. Paroxysmal fibrillation has occurred in 1 of our cases (W. L.) on a number of occasions during the past 7 years and, although the deformity might have been a predisposing etiologic factor, all the attacks have apparently been precipitated by gastrointestinal upsets. The cardiac rhythm in all other cases has been normal.

Because of the deformity, the right border of the heart is difficult to determine by percussion, but the apex is usually found to the left of the midclavicular line, occasionally as far as the axillary line. Pericardial friction sounds have been described by Smith[26] but were not elicited in any of our cases. In Case 7, however, there is a history of rheumatic pericarditis in childhood. Systolic murmurs were heard in 5 of our cases. Four were soft, blowing, not transmitted and no special significance could be ascribed to them. One (Case 9) was heard in the region of the tricuspid valve, but only in the upright position. It was rather rough, markedly influenced by respiration and disappeared immediately when the recumbent position was assumed.

Responses to exercise tolerance tests were good in all the uncomplicated cases except in Case 10. Although the heart rate remained somewhat accelerated and there was some dyspnea on exertion, one is scarcely justified in ascribing these reactions to congenital funnel breast in a man aged 69 years.

German authors[1,12] consider patients with funnel chest susceptible to pulmonary complications, especially bronchitis and tuberculosis. In this country Shively[27] reported 17 cases of funnel chest, and of these 10 had active tuberculosis. However, all his cases were seen in tuberculosis sanatoria. None of our cases gave a history of frequent colds or pulmonary disorder nor was there any evidence of active tuberculosis found on clinical examination.

Fluoroscopic Examination. The heart in cases with moderate or severe deformity tends to be displaced to the left and usually upward, the amount of displacement depending upon the size, shape and position of the deformity. In severe cases the apex may reach the anterior axillary line, but in mild cases little if any displacement is observed. (Fig. 4.) Pericardial and mediastinal

adhesions[28] may prevent displacement of the heart or cause it to be drawn to the right. Case 7 failed to show any displacement, and because of the history of pericarditis in childhood adhesions were considered as a possible explanation. Occasionally the deformity is preponderatingly left-sided rather than nearly symmetrical, and under these circumstances the heart is either displaced or rotated to the right. (Fig. 4.) Usually, however, the right border of the heart is close to or lost within the shadow of the spine. The under surface of the heart can be seen to an unusual extent and in some cases it is raised from the diaphragm so that in inspiration a clear space is seen between the two. The heart appears somewhat larger than normal, but unlike hypertrophied hearts, which are denser than normal, appears more transparent. The lateral view shows the heart and chest to be extremely narrow, which would account for its unusual transparency in the anteroposterior view. Rösler,[29] in a study of normal hearts, found the ratio of the anteroposterior to the transverse diameter to be about 0.7 to 1. In funnel chest this ratio is often reduced to 0.5 to 1, or less. Instead of the sternum forming the anterior chest border there is a large air-containing space formed by the bulging right and left chest. Behind this the deformed sternum can be seen. Occasionally, because of the asymmetry of the depression, the heart can be seen pulsating in front of the plane of the sternum.

Electrocardiographic Study. The electrocardiograms showed no definite abnormalities which could be attributed to the funnel depression. The one of the aged individual showed a left axis deviation and evidence pointing to depression of myocardial function, but in a person aged 69 years these changes cannot be ascribed to a funnel depression.

Case 9 showed a conduction defect (P–R interval, 0.24 second) but this cannot be attributed to the funnel depression. The right axis deviation observed in this case may have resulted from rotation of the heart produced by a primarily left-sided funnel depression.

The electrocardiograms of the other 7 uncomplicated cases were normal, and did not show axis deviation, probably because the heart as a whole was displaced upward and to the left without rotation of its electrical or anatomical axis.

Summary. Ten cases of moderate or severe funnel chest were studied in order to determine its effect upon the heart. There were 9 males and 1 female. The ages ranged from 7 months to 69 years. The deformity was probably acquired in 4 cases, in 5 congenital and in 1 unknown. One case was complicated by a kyphoscoliosis and pigeon breast. Clinically the latter was the only one who showed evidence of cardiac decompensation, but it is believed this was due to the lung lesions resulting from the spinal deformity. Electrocardiograms were normal in 7 uncomplicated cases. Two cases showed evidence of depressed myocardial function. Fluoro-

scopically the heart was flattened in the anteroposterior diameter and correspondingly enlarged in the anteroposterior view; it was displaced upward and to the left, and in 1 case appeared rotated to the right.

Conclusions. 1. Funnel chests of moderate and severe grades are not as uncommon as the meager literature would lead one to believe. Mild degrees of funnel chest are common.

2. Funnel chest of moderate or severe grades causes a displacement of the heart to the left and usually upward. The heart is enlarged in its transverse diameter, but the anteroposterior diameter is decreased. Occasionally the heart is rotated by a marked asymmetrical depression.

3. Although the heart is displaced, electrocardiograms fail to reveal any consistent deviation of the electrical axis, probably because the heart is displaced as a whole.

4. Uncomplicated funnel chest does not appear to have any clearly defined effect upon the functional capacity of the heart unless the deformity is traumatic or of rapid development.

5. The lack of symptoms can probably be explained by the slow development in the vast majority of cases. This allows for accommodation within the chest and heart.

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GROSS CARDIAC HYPERTROPHY IN MYOCARDIAL INFARCTION.*

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There seems to be considerable disagreement in the literature as to whether severe coronary disease and cardiac infarction do or do not produce cardiac hypertrophy. We recently reported 2 cases of cardiac infarction affecting young persons, in which there was marked gross cardiac hypertrophy. The impression given in the literature, and these 2 striking cases, prompted us to make this study, which consisted of a review of 8912 records of necropsy. Out of this number of records of postmortem examination, we obtained 42 in which there was evidence that the coronary arteries had been diseased sufficiently to produce definite chronic infarction.

In selecting this material we excluded all cases in which there was any condition that is known or is supposed to produce cardiac hypertrophy. We excluded all cases in which there was hypertension or a history of blood pressure of more than 150 mm. of mercury systolic, and 90 diastolic. That is, we took a reading of 150 systolic and 90 diastolic for our upper limit of normal. There were 9 of these cases that had been observed over a period of several

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years. Some of the patients had had only one reading of blood pressure, and of course we cannot be absolutely sure that some of them had not had hypertension in the past, although when they

TABLE 1.—SUMMARY OF CARDIAC WEIGHT OF PATIENTS WITH MYOCARDIAL INFARCTION.*

I	II	III	IV	V	VI	VII	VIII
						Increase.	
Case.	Age, years.	Body weight, pounds.	Cardiac weight, gm.	Calculated normal cardiac weight, gm.	Cardiac weight, +8 per cent for error.	Percentage (column VIII column VI).	Grams (column IV minus column VI).
1	35	183	715	357	385	85	330
2	36	141	540	275	297	81	243
3	41	185	368	361	381		
4	46	200	600	390	421	42	179
5	47	120	385	234	251	54	134
6	48	161	475	314	339	40	136
7	50	163	275	318	343		
8	50	170	460	332	358	28	128
9	51	160	650	309	333	95	341
10	52	200	487	387	411	18	76
11	55	145	466	283	315	47	151
12	54	154	411	301	325	26	86
13	54	153	486	296	319	52	190
14	54	120	332	234	252	31	80
15	54	198	355	387	418		
16	55	168	388	328	354	9	34
17	56	135	480	263	284	68	196
18	56	125	338	240	259	30	79
19	56	170	400	331	357	12	43
20	57	181	520	353	381	36	239
21	57	140	475	273	294	61	181
22	59	150	425	293	316	34	109
23	59	166	580	322	347	38	233
24	59	136	364	265	286	27	78
25	59	111	278	216	233	15	45
26	60	208	598	406	438	35	160
27	60	165	514	322	347	48	192
28	60	197	420	304	328	28	92
29	61	148	540	288	311	73	229
30	61	163	530	318	343	54	187
31	65	136	325	266	287	13	38
32	66	195	578	378	408	41	170
33	67	136	412	265	286	44	126
34	67	146	295	285	307		
35	67	119	450	232	250	80	218
36	69	147	295	287	309		
37	70	145	450	283	305	47	145
38	72	115	265	224	242	9	23
39	72	118	373	228	246	51	127
40	72	140	614	273	294	108	320
41	74	134	470	261	281	67	189
42	75	180	420	351	378	10	41

* All patients were men.

were examined at the clinic their readings of blood pressure were normal. We believe it is not unreasonable to assume that if these patients previously had had hypertension that was severe enough to produce cardiac hypertrophy, either they themselves would have been aware of it, or some evidence of it would have been revealed by examination. We excluded all cases of chronic valvular disease, all cases of syphilitic aortitis with aortic insufficiency, all cases of congenital heart disease, and all cases of hyperthyroidism, nephritis and pericarditis (except the pericarditis that occurred with the infarction). We also excluded cases of emphysema and of marked fibrosis of the lungs, and all cases of severe anemia. .

All the patients were men. Their ages at the time of death varied from 35 to 75 years. Two were between 35 and 39 years of age; 4, between 40 and 44 years; 19, between 50 and 59 years; 11, between 60 and 69 years, and 6 between 70 and 79 years. Roentgenologic studies of the hearts were made in 30 cases: Thirteen were reported to be moderately to markedly enlarged; there were 17 cases in which the roentgenologic report revealed no enlargement. There were 25 cases in which the heart was the primary cause of death, and in 17 cases it was not.

It has been proved and accepted by investigators that there is definite ratio between the normal weight of the body and the normal weight of the heart. Large persons normally have large hearts and small persons small hearts. For example, a heart weighing 400 gm. taken from a man who weighed 200 pounds may be well within the limits of normal for that man, but a heart of this weight, taken from a woman who weighed 105 pounds, would be almost double the normal weight for her. The ratio is 0.43 for adult men and 0.40 for adult women. The ratio is slightly higher than normal among thin persons and lower than normal among obese persons. The normal weight of the heart of the adult may be deduced from the body weight with an error of about 8 per cent. The coefficient is not so accurate among persons whose bodies are extremely obese or extremely light. We believe it is not possible to make an accurate study of cardiac weights without considering body weights.

In this series of 42 cases, the weights of the heart were in excess of normal in 37 cases (88 per cent). There were 5 patients whose cardiac weights were well within the limits of normal. The largest heart weighed 715 gm.; the smallest, 265 gm. The greatest relative increase was in a case in which the heart weighed 614 gm.; an increase of 341 gm., or 108 per cent, and that is allowing for an error of 8 per cent, as has been shown previously. There was another heart that weighed 715 gm.; in this case, the absolute increase in weight was 358 gm., but the percentage increase was 85 per cent after allowance was made for a probable error of 8 per cent.

Our data are summarized in the table. In 5 cases, the cardiac weight was normal. Otherwise, the minimal increase above normal

is 9 per cent and the maximal increase, 108 per cent. The average increase for the whole group is 44 per cent.

Summary and Conclusions. A study has been made of the weights of the heart in 42 cases of cardiac infarction, in which all other known or supposed causes of cardiac hypertrophy have been excluded. Of the 42 cases, in 37 (88 per cent) there was definite gross cardiac hypertrophy. In 5 cases the weights of the hearts were not above normal. The minimal increase in weight was 18 gm. (9 per cent); the maximal increase, 341 gm. (108 per cent), and the average increase, 132 gm. (44 per cent). From the data given it would appear that cardiac infarction is a definite cause of cardiac hypertrophy.

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SPONTANEOUS RUPTURE OF THE AORTA.

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This title might suggest that under certain circumstances the normal aorta ruptures through inability to withstand the ordinary pressure within it. There has been much controversy about this point, some stoutly maintaining that the undamaged aortic wall may at times be placed under such stress as to give way in sudden and fatal hemorrhage, while others are equally convinced that no spontaneous rupture is possible without antecedent damage or degeneration of the vascular tissues. It is obvious that in discussing the condition of spontaneous rupture, we must confine our attention to those instances in which no antecedent clinical or pathologic evidence of a progressive lesion was noted, and in which also no unusual extraneous factors have imposed themselves, which could be held directly accountable for the severe tissue lesion and fatal hemorrhage. Thus, we omit those cases that follow falls from considerable heights (buildings, aëroplanes and bridges). Under those circumstances the aorta, normal or diseased, bursts because of the sudden increase of blood pressure within it resulting from the impact of the blood and from the doubling up and distortion of the body as it strikes the ground. It is the explosive force of the contained blood which rips through the aortic wall. Nor will we consider the

progressive destruction of a syphilitic aortitis which leads to aneurysm and so commonly to sudden fatal hemorrhage or to slow leakages into neighboring hollow viscera and body cavities. Occasionally what appear to be cases of spontaneous rupture of the aorta are shown to have had their hemorrhage from unrecognized and obscure aneurysms. Some authors have preferred the term "idiopathic" in place of "spontaneous" rupture of the aorta, preferring the meaning "without apparent extrinsic cause" to that of "unassociated."

The majority if not all cases of spontaneous rupture of the aorta are associated with some degree of dissecting aneurysm. This need not always be the case, but as we shall indicate later, the conditions which predispose the aortic wall to dissecting aneurysm are the same as those which permit the vessel to suddenly give way in rupture. In truth, every dissecting aneurysm is an incomplete rupture of the aorta.

If, then, we are able to determine the underlying factors which predispose a vessel for the development of a dissecting aneurysm, we shall be able to understand the causes which play a part in a large proportion of spontaneous ruptures. Not all cases belong to this class, as there are other conditions which independently predispose the aorta to rupture. These may be classified as: (1) Trauma; (2) acute mycosis of aorta; (3) exogenous erosion of aorta (tuberculosis or abscess); (4) syphilis of aorta, and (5) vermicular infestation of the aorta (as seen in spirocerca infection of dogs). Here the reason for the rupture of the aorta is obvious and cannot be classed as spontaneous or idiopathic. But in the remaining group, where no clinical or pathologic factor is demonstrable to the naked eye, and where the patient has shown no progressive ill health, the explanation for the occurrence of sudden fatal hemorrhage is frequently difficult to indicate.

It is apparent that, if a dissecting aneurysm is an incomplete rupture of the aorta, a certain proportion of the cases of complete rupture will have begun as the usual dissecting aneurysm, but continued to the production of a perforating tear. This is true in the greater number of cases, and particularly of those above the age of 40. Dissecting aneurysms are usually found after 40, the relative incidence increasing with advancing years. A dissecting aneurysm begins as a tear through the inner layers of the aortic wall, then by separating the layers of the outer part of the media it excavates a cavity in a longitudinal and circular manner. The dissecting aneurysm may perforate outwardly through the remaining portions of the aorta, or it may perforate inwardly to communicate again in its distal portion with the aortic lumen. When external perforation has not completely ruptured the vessel, the dissecting aneurysm does not lead to immediate death, and its cavity may be reclothed by an endothelial membrane. The literature contains upward of 350 cases of dissecting aneurysm. One feature in true

dissecting aneurysm is constant: the dissection of the aortic wall giving rise to the aneurysm has taken place between the lamellæ of the media, usually in its middle or outer third. Blood masses lying in the loose stroma along the course of the aorta, even though communicating with the aortic lumen, are not true dissecting aneurysms. Furthermore, syphilis of the aortic wall is not a factor in the production of true dissecting aneurysms, as the very nature of the syphilitic process with its gumma and fibrosis does not render the vessel liable to dissection. In fact, the granulomatous inflammatory invasion of the arterial wall will tend to weld the neighboring laminæ more closely together so that the wall may be less readily split into its anatomic layers than normally.

Considering the structure of the wall of the aorta, the normal intima is a delicate layer superimposed upon the internal elastic lamina with its stratum of longitudinal muscle fibers. The media is the important structure, composed of alternating elastic bands and circular muscle fibers. It is relatively thick and endowed with great strength. In its outer third it is supplied by an abundance of small bloodvessels, the vasa vasorum, which are distributed to it from the adventitia. These nutrient vessels have their origin from different small branches arising from the aorta, such as the coronaries of the heart, the intercostals, the vessels of the neck and the various abdominal arteries. Woodruff has recently demonstrated small nutrient vessels arising directly from the aorta itself; Robertson, in our laboratory, has found similar vessels. The inner two-thirds of the media of the human aorta contains no bloodvessels. It has been noted that, with disturbances of the vasa vasorum, marked changes may occur in the portion of the aorta nourished by them. The outermost portion of the media is bounded by an irregular mass of elastic fibers, spoken of as the external elastic lamina. Beyond this layer lies the adventitia made up of a matting of connective tissue, elastic fibers, some muscle cells and small bloodvessels.

As the strength of every artery lies in the strength of its medial coat, it is obvious that whenever aneurysm develops upon a vessel, the middle coat has been damaged. The pouching, stretching or ripping of the arterial coat is induced by the blood pressure acting upon an area of weakness. What is true, in general principle, for aneurysm is also true for rupture of the aorta. However, the question frequently arises: how far is the heightened blood pressure alone responsible for the rupture of an apparently normal artery? We have examined the aortas of individuals between the ages of 20 and 40 and subjected them to pressures of 1000 mm. of mercury without producing rupture. Oppenheim states that rupture of the aorta will not occur until a pressure in the neighborhood of 3000 mm. of mercury is reached, a pressure about 20 times that of normal. As these analyses were all determined at postmortem when the vessels were in a state of cadaveric rigidity it is possible that the

figures will differ from those necessary to burst a living vessel. This point was investigated in the aortas of rabbits by Schnurbein who found no difference in the resistance to pressure between the aortas of freshly killed animals and those showing postmortem rigidity. Hence, one is forced to realize that in the uninjured aorta a tremendous internal pressure is necessary to produce rupture of its wall, a pressure much greater than can be developed by the cardiovascular mechanism alone.

It would seem obvious that damage to the wall of the aorta preceded the occurrence of rupture; but a number of cases, about 40 in all, have been reported in individuals under 40 in whom no adequate explanation is available. Let us dismiss from consideration all cases over 40 years, for in them there is always some degenerative change in the muscle and elastic elements of the media. A vessel so afflicted no longer possesses its juvenile pliability, and the arterial coat is actually more friable. readily splitting into two lamellæ through the media. The aorta of a child or youth maintains its normal elasticity for some hours after death, and such an aorta has its several layers of tissue firmly bound together so that they cannot be separated. The aortas of old age possess an unusual dryness and friability which, in a measure at least, account for the tendency to develop dissecting aneurysms and spontaneous ruptures.

Below the age of 40 or thereabouts, the presence of well-marked degenerative changes in the media, sufficient to show a weakness in the union of the neighboring laminæ, is unusual. It is in these in which occasionally a sudden rupture of the aorta takes place and an examination of the wall may fail to reveal an adequate lesion.

A number of authors have observed an hypertrophy of the heart in association with rupture of the aorta (Busse, Schlipp). The presence of the hypertrophied heart is taken as evidence of an increased blood pressure. Furthermore, others have noted the occurrence of chronic nephritis in a certain number of these cases. However, the cases in which the evidences of chronic cardiorenal disease were noted were individuals beyond middle life, in whom a certain amount of heart and kidney disease is not unusual. In a few others a more direct relation could be associated with the presence of a narrowing of the aorta just above the level of the ductus arteriosus. This condition of coarctation of the aorta is accompanied by a dilatation of the ascending limb and arch of the aorta along with an hypertrophied heart. Enlargement of the anastomosing systemic vessels is usually present and there is adequate evidence, that the portion of the aorta which is in direct continuity with the heart suffers a definite increase in blood pressure. Degenerative changes may then involve these aortic structures, weakening the wall and occasionally leading to rupture.

Babes and Mironescu observed the occurrence of rupture and dissecting aneurysm of the aorta in a woman aged 51. They believed

that the primary condition was one of hypertension which had gradually led to the production of multiple fissures in the tissues of the media, and by coalescence had so weakened the vessel wall as to allow the occurrence of spontaneous rupture associated with a dissection of the middle coat. The authors were convinced that definite spaces were present in the wall, induced through the influence of high blood pressure. It is difficult to understand how such lesions could develop under the influence of hypertension. Other factors than an increase in blood pressure must be at work before lesions with necroses of muscle cells and elastic fibers can give rise to these faults in the middle coat.

Spontaneous rupture of the aorta has been described in early youth, Rokitansky encountering the lesion in a boy of 8 years, Oppenheimer in a girl of 9 years, Wasastjerna in a boy of 13 years, while quite a number of cases have been reported in individuals of 20 to 30 years of age. Although some of the authors claim to have searched diligently for evidences of lesions in the aortic wall near the site of rupture, and state that they were unable to demonstrate them, one cannot be entirely satisfied that the various methods used for demonstrating changes in elastic fibers, muscle fibers and lesions in the vasa vasorum, have been sufficiently well applied to accept unreservedly the statement that the arterial wall was normal. It is obvious, of course, that if the tear or the dissecting aneurysm, passes through the areas of injury in the aortic wall, little will be left within that tissue to indicate the condition of the structures at the point of the tear. The evidence that the neighboring muscle and elastic fibers show but little change in their character is not sufficient proof that an area of weakness and damage did not lie in the path of the rupture. In a few cases, Babes and Mironescu, Krukenberg, and Bay observed the presence of focal degenerations and necroses in relation to the vasa vasorum in the media. These authors found areas of degeneration, cysts, or hemorrhage in portions of the arterial wall not involved in the rupture or dissecting aneurysm. They believed that these lesions represent the points of weakness and that the splitting of the artery occurred along their path. In some of the cases the vasa vasorum showed obliterating endarteritis, thrombosis, necrosis and hemorrhage, so that a cleft was produced which led to a separation of the layers of the artery and only subsequently did a perforation occur between the lumen of the vessel and the cavity within its wall.

Recently Gsell, studying a number of cases of rupture of the aorta, found that the vessel wall had suffered noninflammatory necrosis of the media. He compares the lesions to those previously described by Wiesel, who had noted the presence of peculiar focal necroses in the vessel wall of young individuals dying of acute infections. It is suggested that these necroses are the result of toxic damage of the muscle elements along with changes in the elastic tissues. They have no direct relation to lesions arising in the intima.

Erdheim in a careful study of a case of spontaneous rupture observes lesions similar to those described by Gsell and notes that patches of necrosis and peculiar hyalin vacuolization of the media were present in the aortic wall beyond the region of rupture. The muscular elements as well as the elastic fibers and connective tissues were involved. The absence of an inflammatory reaction was striking and there was little attempt at repair. The necroses were particularly evident in the outer two-thirds of the media. The destructive process in the media leads to disintegration of the cellular elements and the dissolved materials are absorbed without local tissue reaction. These areas may subsequently become infiltrated by an albuminous fluid leading to peculiar cystic spaces between neighboring elastic fibers. These findings were supported in a further investigation by the same author, who studied more carefully the mucoid degeneration of the wall and the development of necrotic cysts. He carefully differentiates the process of necrosis of the media from the process of mucoid degeneration, but is unable to clearly determine the factors of causation although he points out the possibility of toxins playing an important rôle.

In 5 cases of spontaneous rupture, which came to our attention, somewhat similar lesions were encountered, which we believe played a part in the subsequent rupture and fatal hemorrhage of the aorta. In each case a dissecting aneurysm had occurred along with the rip of the aorta.

Case Histories. CASE 1.—S. W., a female, aged 23 years, was pregnant about 8 months and felt well until midnight of October 19, 1925, when she suddenly developed a terrible attack of anginal pain confined to the precordium and radiating to the left back. This attack was associated with marked dyspnea and the sensation of choking. The pain, which was partially relieved by morphin, lasted 2 or 3 hours and recurred on the following two nights when she had some vomiting.

She had scarlet fever at the age of 6, and influenza in 1918. No history of rheumatic heart disease or of syphilis.

The patient was admitted to the Hospital on October 22d, stating that she was free from pain. The pulse rate 110 with extrasystoles every third or fourth beat; slight systolic and diastolic murmurs in the aortic area. No cyanosis, no edema of extremities; liver not enlarged and lungs clear. Temperature was normal, respirations 20 to 28. Wassermann reaction negative. Blood pressure 110/50. Patient was kept in bed. Five days after admission she had dyspnea, cyanosis, but no pain. She died suddenly while resting quietly in bed on October 31st, 12 days after the onset of the attack.

Autopsy. The body was that of a young, adult, white female, with the signs of pregnancy, enlarged breasts and enlarged uterus containing a fetus of about full-term proportions.

The *lungs* were found normal except for a few old pleural adhesions.

The *pericardial sac* was markedly distended and tense and filled with 600 cc. of fluid blood.

Heart and Aorta. The heart was about usual in size, and was surrounded by the fresh clotted blood within the pericardial sac. There were no adhesions or signs of recent inflammation in the pericardium. The epicardium

contained a fair amount of yellow fat. At the root of the aorta just above its junction with the base of the heart, there was a slitlike perforation 0.8 cm. in length which entered the aorta and freely communicated with the pericardium. It lay along the left anterior aspect of the root of the aorta in close proximity to the pulmonary artery. The edges of the rupture were sharp, as if made by a knife; the external surface of the opening showed a slight blood infiltration of the surrounding tissue and had the character of a recent tear. Upon opening the heart the cavity on the right side was normal; the tricuspid measured 9 cm., the pulmonary 5 cm. They were thin and elastic and were without change. The left ventricle showed some hypertrophy, being 2 cm. in greatest thickness. The mitral valve measured 8.5 cm. and showed a slight amount of transparent thickening close to the free margin.

In approaching the aortic orifice from the left ventricle a peculiar appearance presented itself prior to cutting the ring. It was found that the aortic leaflets were invaginated into the conus of the ventricle, suggesting prolapse not only of the leaflets themselves, but also of the tissue of the aortic ring upon which valvular structures were attached. The entire aortic orifice appeared to be blocked by a mass of tissue projecting from the aorta.

Aorta. An annular transverse tear was found in the base of the aorta at a distance of 0.5 cm. above the aortic leaflets. The tear was sharp and its edges appeared as if made by a knife; it passed completely about the circumference of the aorta save for a small bridge 0.5 cm. in width which maintained the continuity between the proximal and distal portions of the aorta. The rupture of the aortic tissue occurred only in transverse direction and did not produce stellate tears. The tear through the aortic wall was not complete, but entered the deep portion of the media and then led to a peeling off of the proximal portion of the aortic wall so as to produce a local dissecting aneurysm. The dissection of the aortic coat extended from the transverse tear toward the aortic ring, excavating the inner two-thirds of the aortic wall behind the sinuses of Valsalva and down to the lower edge of the aortic cusps. The dissecting aneurysm was 3.5 cm. in its greatest length. Thus a collar of a dissecting aneurysm occupied the base of the aorta. The aneurysm did not progress beyond the coronary arteries, both of which were given off from the aorta above the level of the left posterior aortic valve cusp. In the cavity of this recent dissecting aneurysm there was some fresh, slightly adherent clot. The walls of the aneurysmal pouch were clean and pink in appearance. In some places a thin film of fibrin could be seen covering the surface. The walls of the aneurysm, in the vicinity of the perforation, showed a great quantity of this grayish deposit. The perforation which extended from the lumen of the aorta to the pericardium was found to lie within the area of the aneurysm and to possess a slitlike orifice around which there was no evidence of thrombus or an inflammatory exudate. There was no evidence of dissection of the aortic tissue in the upper direction, but it was found that immediately above the point of perforation the tear had entered the loose tissue lying between the aorta and pulmonary artery. There were some superficial fatty streaks in the descending thoracic aorta. The aorta was elastic and of usual consistency for a young individual showing no evidence of syphilis, arteriosclerosis or atheroma. There was nothing to indicate, in the naked-eye examination, an antecedent disease process with which the tear of the aorta and separation of the aortic coats could be associated.

Anatomic Diagnosis. Rupture of ascending aorta; laceration of aorta; hemopericardium; dissecting aneurysm of aorta (slight); old bilateral pleural adhesions; pregnancy; (sudden death).

Résumé. This was a case of sudden death in a pregnant woman of 23 years, in whom an extensive rupture of the aorta had taken place without

the presence of macroscopic change in the aortic wall. She suffered a severe anginal attack 12 days before death and continued in distress, save as relieved by morphia. She had no acute infection and the Wassermann reaction was negative. Blood pressure 110/50. She died suddenly while resting in bed. The autopsy revealed a transverse tear of the aorta 0.5 cm. above the aortic cusps. Below the level of the aortic tear a dissecting aneurysm was produced reaching to the insertion of the aorta upon the heart. A small perforation extended from the dissecting aneurysm into the pericardium leading to the filling of the pericardial sac with blood.

CASE 2.—R. M., male, aged 45 years, a salesman, was admitted to hospital May 23, 1927; for six weeks he had suffered headaches and attacks of vomiting; also had frequency and hematuria. One week later he complained of dimness of vision which became steadily worse. In 6 weeks lost 10 pounds.

Patient is stuporous, speech slow, no respiratory distress. Respiratory system showed nothing of note. Cardiovascular system, apex beat 10 cm. from midline in 5th interspace; blowing systolic mitral murmur; pulse regular; radial, brachial and femoral arteries palpable and thickened; blood pressure 210/140. Liver slightly enlarged. Urine, 24-hour specimen 960 cc.; acid, specific gravity 1016, albumin present, blood present, granular casts. Wassermann reaction negative. Patient died suddenly 4 days after admission.

Autopsy. The body was that of a well-developed and well-nourished middle-aged man. The external surfaces of the body showed a number of ecchymoses of the skin, but otherwise nothing of note.

The *heart and pericardium* occupied an area measuring 14 cm. in length by 16 cm. in width. Both pleural cavities were free from adhesions and excess fluid. The pericardium was smooth and glistening. The heart lay free in its cavity which contained a large amount of dark red recent clot which entirely surrounded the heart. It was distinctly enlarged, particularly on the left side but also to some extent on the right. It measured 12.5 by 15 by 7.5 cm. There was a fair amount of epicardial fat. The epicardium showed no evidence of recent or old inflammatory change. The left ventricle measured 2.75 cm. in thickness and was fairly well contracted. The musculature was firm and dark red and there were no areas of fibrosis. The valve orifices measured, tricuspid, 12 cm.; pulmonary, 7 cm.; aortic, 7.5 cm.; mitral, 10.5 cm. The leaflets were thin and elastic with no evidence of old or recent inflammation. The coronary arteries were patent throughout, showing occasional yellow atheromatous plaques along the course of the main branches.

Aorta. The ascending aorta measured 7 cm. in circumference. The wall appeared to be of usual thickness and the inner surface was quite smooth, save for a few stippled areas of fatty change. In the transverse arch and continuing into the descending arch, there was considerable nodular endarteritis and atheroma, particularly in the vicinity of the outlet of the vessels of the neck. The important lesion in the aorta lay in the ascending aorta 3.5 cm. above the aortic cusps. This portion of the aorta showed the least amount of intimal change. The lesion consisted of a transverse tear of the aortic wall 2 cm. in length. This tear was sharp and knifelike, passing through the entire thickness of the aorta but at the right border leading into a pocket of a dissecting aneurysm. The borders of the tear showed no evidence of ulceration, inflammation or deposition of fibrin. In the vicinity of the tear and for about 2 cm. toward the aortic cusps the wall was seen to be more translucent than elsewhere. The tear had progressed through the media and adventitia, entering the loose tissues between the aorta and the pericardial sac. Blood had escaped through the rupture, causing a hematomatous protrusion beneath the pericardium and outside of the aorta, meas-

uring about 5 by 6.5 cm. At one point was found an opening through the pericardial covering, through which the blood had escaped into the pericardial sac. In dissecting the aorta on its outer surface, it was found that the sac which had formed outside the area of rupture had actually dissected some of the tissues of the aortic wall, and that the covering was not merely composed of loose pericardial structure, but included the outer layers of the aortic wall. On exploring this outer sac, it was found to extend from 1 cm. below the origin of the innominate artery, encircling the right border of the ascending aorta downward to the point of insertion of the aortic valves. The inner surface of the cavity showed the striations of the circular muscle bundles of the aortic wall. Upon these surfaces, a thin film of fibrin had been deposited along with small blotches of red blood. There was, however, within the cavity no evidence of a thrombus. On viewing the rupture from the posterior surface, it was found that the tear was not as clear cut as would appear from the intimal side, but had passed through succeeding layers of muscle tissue, raising successive lamellæ of these structures during the passage. The manner in which the layers of the media had been separated from each other, bringing about a division of the media in its outer third, was quite similar to the appearance which we encounter when the aorta of an elderly person is divided into two parts by splitting the media and stripping these coats apart. The appearance which we found in this specimen suggested the presence of a potential, but not actual, cavity in the outer portion of the media and that the rupture through the inner wall (consisting of the intima and inner two-thirds of the media) was only a final event in an inherently weakened wall. On carefully exploring the sac in a downward direction, it was found that it passed to the aortic ring and encircled the right coronary artery. It was noted that the dry and brittle character of the aorta extended beyond the sac of the dissecting aneurysm, for it was possible to continue the separation of the wall of the aorta by moderate tension upon the walls of the sac.

Anatomic Diagnosis. Rupture of aorta; hemopericardium; chronic nodular endarteritis of aorta and atheroma of coronary vessels; hypertrophy and dilatation of heart; chronic interstitial nephritis; dissecting aneurysm of aorta.

Résumé. A man, aged 45 years, suffering from chronic Bright's disease and having a high blood pressure, died suddenly without symptoms referable to the heart. Wassermann reaction negative. At autopsy there was disclosed a transverse knifelike rupture of the aorta 3.5 cm. above the aortic valve. The rupture led to the development of a local dissecting aneurysm, the perforation of which into the pericardial sac had caused death. The aorta at the site of rupture was thinner than normal, due to bandlike necroses occupying the media.

Case 3.—Mrs. M. B., aged 54 years, has suffered from headaches for 4 years. Recently these have been increasing and accompanied by vomiting. She has had a history of rheumatism and recurrent attacks of precordial pain. On April 14, 1931, she was suddenly seized with a severe pain in the neck, rapidly spreading to the shoulders and to the chest. The pain became so severe that she required morphin and she vomited. Temperature 99.4°, pulse 86, and respirations 22. Lungs, negative. Heart, slightly enlarged; occasional extrasystole. Blood pressure, 190. Palpable vessels somewhat sclerosed. Abdomen, negative. Wassermann test negative. Blood: white blood cells, 20,500; polymorphonuclears, 90 per cent.

The dull pain across chest persisted from day to day. There was dullness at the base of the left lung; a friction rub was heard at the apex of the heart. Aspiration of the left chest yielded 250 cc. of blood-stained fluid. On April 30th, while taking a bath, the patient suddenly collapsed and died, 16 days after onset.

Autopsy. The body was that of a well-developed middle-aged woman, in whom the main findings at necropsy were related to the cardiovascular system. Within the chest the outstanding feature was an enormously ballooned pericardium measuring 18.3 cm. in width, and filled with a large mass of fluid and recently clotted blood.

Heart and Aorta. The heart and aorta were kept attached as one specimen. Some of the clotted pericardial blood had developed tough fibrinous attachments to both the parietal and visceral pericardium. It was possible to distinguish blood which had been evacuated just prior to death, and some which had been emitted some days ago, and whose fibrin was in the early phase of organization. The pericardial sac showed no evidence of a primary inflammatory process. The heart lay enveloped in the mass of blood, so that none of its surface could be seen. On exploring the pericardial sac at the base, it was found that there was a laceration at a point immediately above the level of the left ventricle, where this structure was inserted onto the base of the aorta.

The *heart* was firmly contracted. The wall of the left ventricle was quite thick (2.5 cm.) and firm. The cavity of the left ventricle was small, not dilated, and showed some white patches of pearly endocardial thickening. The aortic orifice measured 5.5 cm. and the aortic valves were normal. The mitral orifice was not narrowed, but the edge of the cusps were slightly thickened and on the posterior surface were some fatty plaques. The pulmonary orifice measured 5 cm. and was normal. The tricuspid orifice measured 9.5 cm. and showed no change. The heart muscle showed numerous patches of fibrosis, particularly along the endocardial border. The coronary artery showed some sclerosis but no marked narrowing of the lumen was observed.

Aorta. On opening the aorta it was found that its wall had been split into a double layer from the aortic ring to its bifurcation in the abdomen. Into this space there had been an escape of blood which encircled the aorta in all its parts. This formed a layer of varying thickness, the greatest being found at the arch, where it measured 1.5 cm. and was interposed over its convex portion. This dissecting aneurysm encircled the vessels of the neck and surrounded the mouth of the innominate artery; otherwise it did not extend along any of the branches coming from the aorta. It had its beginning in a transverse tear within the intima of the arch of the aorta immediately opposite to the origin of the innominate artery, 9 cm. above the aortic valves. The tear across the aorta was 5.5 cm. in length and involved the aorta in more than three-quarters of its circumference. At the point of tear there was no evidence of atheroma or ulceration. The rupture was a single linear division with sharp knifelike edges. The tear led through the intima into the media where the separation took place leading to the dissecting aneurysm. The inner wall of the dissecting aneurysm formed a layer about the thickness of ordinary blotting paper, while the outer wall, composed of the outer part of the media, adventitia and periadventitial connective tissues, was thicker than the inner boundary.

The aneurysm caused a considerable bulging in the ascending limb of the aorta and gave rise to a protrusion of the aorta within the pericardial sac. Over this bulging mass the outer coat of the dissecting aneurysm had given way and led to hemorrhage into the pericardium. Furthermore, the mass of blood occupying the dissecting aneurysm at the root of the aorta led to an irregular bulging of the intima narrowing the lumen of the aorta.

The intimal surface of the aorta was clear and without evidence of change in its first portion up to the point of rupture in the arch. From this point onward, there was a nodular endarteritis, particularly about the exit of the intervertebral arteries. These nodular thickenings were smooth and pearly white, many with some atheroma about them. Between these pearly

nodules the wall of the aorta was wrinkled and in places showed a peculiar atrophic depression of the surface. These intervening portions were more transparent than normal and suggested an actual loss of tissue in their bases. The longitudinal wrinkling at first sight suggested a syphilitic process, but on closer examination it was noted that no stellate scars were present.

The blood lying in the dissecting aneurysm was found laminated and well clotted. In some regions the clot was very adherent to the walls and appeared older. Furthermore, it was noted that the outer wall of the dissecting aneurysm with its periadventitial tissues was edematous and thick.

Anatomic Diagnosis. Rupture of aorta; dissecting aneurysm of aorta; hemopericardium; hypertrophy and dilatation of heart; chronic nodular endarteritis of aorta and coronary arteries.

Résumé. A woman, aged 54 years, with a history of rheumatism and recurrent precordial pain, was suddenly seized with an anginal attack which was relieved by morphin. Although fairly comfortable for a period of 16 days she died suddenly with a hemopericardium. The Wassermann reaction was negative. There was a transverse tear of the ascending aorta which led into a dissecting aneurysm involving the aorta from the heart to the iliac arteries. The blood within the aneurysm was undergoing organization, indicating that the aneurysm had been produced some days, probably 16, before death. The final rupture into the pericardium took place at the time of death. The inner aspect of the aorta had a peculiar corrugated appearance, suggesting at first sight a syphilitic process. These areas, however, were depressed and were located over necroses of the media.

Case 4.—Mrs. G. S., aged 39 years, for the past 2 years had suffered from recurrent attacks of dyspnea and palpitation. She had been subject to headaches which had been more frequent during the last 2 weeks. She was pregnant at about the sixth month. On May 13, 1931, she developed a sudden severe pain between the shoulder blades and on the right side of the chest. The right arm and hand became blanched and the veins of the neck and upper chest became engorged. The patient rapidly collapsed as in a state of shock. About an hour after the onset she vomited some fluid containing blood, and 4 hours later she passed blood by rectum. Temperature, 98°; respirations, 38; pulse, 114. Blood pressure 100/30. The heart was found enlarged; a soft presystolic murmur was heard at the apex and a harsh systolic murmur in the second right interspace propagated into the neck. Blood: white blood cells, 12,200; polymorphonuclears, 93 per cent. The patient was stuporous; no evidence of paralysis; lungs show some moist râles. She vomited large quantities of blood-stained frothy fluid and died suddenly 13 hours after onset of acute symptoms.

Autopsy. The body was that of a middle-aged woman, about 6 months pregnant, in whom the outstanding pathologic findings were related to the heart and aorta.

Each *pleural cavity* contained about 500 cc. of a clear fluid, while the lungs showed some evidence of edema.

The *heart* was distinctly hypertrophied, particularly in its left ventricle. The valve orifices were not narrowed, although both the mitral and aortic cusps showed some thickening along the free borders. Scattered areas of fibrosis were present in the wall of the left ventricle and in the papillary muscles. In the right auricle opposite the insertion of the aorta into the heart was a blotch of hemorrhage corresponding to the base of the dissecting aneurysm, which will be described below. The endocardial surface of the left auricle showed some rheumatic scarring. The coronary arteries showed considerable sclerosis and narrowing, especially the left descending branch and the main trunk of the right coronary.

Aorta. The ascending limb immediately above the aortic ring measured 9.5 cm. in circumference. The inner surface was smooth, showing only

slight superficial deposits of fat. At a point 1 cm. above the level of the insertion of the aortic cusps was a transverse tear almost completely encircling the aorta except for a narrow isthmus 1.5 cm. in width. This tear was of recent origin, its edges were sharp and it passed through the inner two-thirds of the thickness of the aorta into a recently developed sac, which was filled with fluid blood and a few stringy coagula. A dissecting aneurysm was thus formed, completely enveloping the aorta, bounded on the outer side by part of the media and the adventitia. The dissection had occurred toward the heart, passing behind the sinuses of Valsalva down to the insertion of the aorta into the myocardium. It had also encircled the margin of the anterior coronary artery. There was no old clot within any portion of the dissecting aneurysm. The aneurysm had not burst into the pericardial sac.

The dissection had progressed distally from the heart along the entire course of the aorta, in some places completely encircling the vessel, while in others it extended only partially around its circumference. Opposite the bifurcation of the trachea there had been some escape of blood into the neighboring soft tissues. Within the cavity of the dissecting aneurysm, which throughout was composed of the divided wall of the aorta, there was some fluid blood and some recent coagulum. In those portions where the splitting of the laminæ had not led to pouching it was noted that the tissues could be separated with remarkable ease in the manner in which the dissecting aneurysm was produced. The dissection was followed down to the bifurcation and extended for a short distance into the wall of the iliac arteries.

On viewing the aorta from its inner surface, very little change of the intima was noted in its thoracic portion. A few small diffuse areas of endarteritis and some splashes of superficial atheroma were noted, also some peculiar groups of longitudinal grooves, somewhat suggesting syphilis but lacking the stellate character. Some escape of blood was noted into the soft tissues about the crus of the diaphragm.

The abdominal aorta showed marked sclerosis of its wall below the level of the renal arteries. This sclerosis consisted of flat calcareous plaques which seemed to lie directly beneath the intima and over which no intimal thickening had occurred. These had the appearance of the small crater-like calcareous plaques seen in the aorta of experimental arteriosclerosis, such as induced by adrenalin, nicotine and other drugs.

Anatomic Diagnosis. Rupture of aorta; dissecting aneurysm of aorta; chronic nodular endarteritis of aorta; arteriosclerosis of coronary arteries.

Résumé. A pregnant woman, aged 39 years, had a history of recurrent attacks of dyspnea and palpitation for 2 years. She developed a sudden attack of angina and died within 13 hours of the onset. The autopsy disclosed a rupture of the ascending aorta leading into a dissecting aneurysm, extending from the aortic valves to the pelvis. The point of rupture showed no inflammatory process nor atheroma of the intima, but there was extensive mucoid degeneration of the media at this point. The dissecting aneurysm followed a course between the middle and outer third of the media. Throughout the aorta there were patches of degeneration of the muscle elements of the outer part of the media. The lesions were similar to those described in previous cases. It was also interesting that a similar type of degeneration was present in the musculature of the renal, splenic and coronary arteries. Inasmuch as the aneurysm was of recent date, no clotted blood was found between the torn areas of the aorta.

CASE 5.—E. C., aged 38 years, was admitted to hospital on May 30, 1931, in a semistuporous condition. He had been in good health until December, 1930, when he developed lumbosacral pain. He also complained of dizziness and double vision. For the previous 2 weeks he had had marked

dyspnea and palpitation on exertion. Occasional attacks of nausea were relieved by vomiting.

Twenty-four hours before admission the patient developed acute abdominal pain with nausea and vomiting. Temperature, 100.6°; pulse, 106; respiration, 20; blood pressure, 220/150. Urine, albumin +++; casts, red blood cells and white blood cells; blood hemoglobin, 110; white blood cells, 19,000; Wassermann reaction, negative.

For the first few days in hospital patient appeared to be improving, but low-grade fever continued. On June 9th he became restless, with some evidence of spasticity of right arm and leg. Later he developed a motor aphasia. June 13th patient suddenly collapsed, and died 5 hours later.

Autopsy. The body was that of a well developed male, showing well-marked cerebral arteriosclerosis with softening of brain in the left hemisphere. There was also a recurrent interstitial and glomerulonephritis. The left pleural cavity was filled with blood.

Heart. The heart was of good size, the epicardium was covered by a fair amount of fat. There was no evidence of blood in the pericardial sac. The valvular orifices appeared normal and there was no evidence of old or recent endocarditis. The myocardium of the left ventricle was very thick, measuring 2.5 cm. The musculature was firm and well contracted. There was also some increase in the thickness of the right ventricle, measuring 0.8 cm. in its mid portion. The sclerosis was diffuse and affected both the right and left coronaries. There was some fibrosis in the left ventricle.

Aorta. The aorta had a remarkable and distorted appearance showing abnormal bulgings at the root of the aorta within the pericardium, as well as over the descending arch on the left side. The bulging mass in the pericardium was of a purplish-red color and consisted of a sac of blood covered by the thin pericardial membrane and appeared ready to burst. This mass was the size of a hen's egg, measuring 5 by 3.5 cm. in diameter.

The mass over the descending arch was still greater in size, measuring 8 by 5 by 5 cm. The surface was covered by the pleura and was hemorrhagic, there being some adherent blood clot protruding into the left pleural cavity. Other bulgings were also noted in the lower portion of the abdominal aorta just above the bifurcation and along the course of both iliac arteries. On opening the aorta the intimal surface of the ascending limb, and the arch were quite smooth and yellowish-white in color, while in the lower portion of the thoracic and abdominal aorta there were some nodular thickenings of the intima.

In the thoracic aorta opposite the level of the first pair of intercostal arteries, there was a knifelike transverse tear on the anterior portion partially encircling the vessel. This tear extended through the inner wall into the cavity between the two lamellæ in an upward and downward direction. This separation or dissection of the aortic wall extended throughout the length of the vessel from the sinus of Valsalva to and including both iliac arteries; the dissecting process also involved the left carotid and left subclavian arteries. The two bulging masses referred to above consisted of large hematomata arising from this dissecting process and leading to the infiltration of the periaortic tissues in both these regions. The hematoma at the root of the aorta measured 2.5 cm. while that over the arch was 4.5 cm. in thickness.

The dissecting aneurysm encircled the aorta in most of its parts with only occasional areas, where the lamellæ remained attached to each other. The blood clot in all portions of the dissecting aneurysm was dark red and friable in nature and of recent origin.

Anatomic Diagnosis. Rupture of the aorta; dissecting aneurysm of aorta; arteriosclerosis of coronary and cerebral arteries; softening of brain; and recurrent nephritis.

Résumé. A man, aged 38 years, suffering from Bright's disease and cerebral arteriosclerosis, died suddenly with no symptoms particularly referable to the heart. The Wassermann reaction was negative. The autopsy disclosed a transverse rupture of the descending thoracic aorta leading to a dissecting aneurysm extending from the heart to the iliac veins. Leakage from this aneurysm took place into the left pleural cavity. There were no lesions of the intima having any relation to the site of rupture. It is probable that the rupture of the aorta and the dissecting aneurysm occurred 15 days before his death. Further evidence of this was obtained on microscopic examination, when a well-established granulation tissue was found to clothe the inner wall of the dissecting aneurysm.

Microscopic Examination of the 5 Cases. To avoid undue repetition in the description of the microscopic characteristics in the aorta, the findings in the above 5 cases will be discussed conjointly. This is also desirable as the quality of the change observed in the aortic wall is similar in all cases, though it varied in its extent. In Cases 1 and 2 the lesions were particularly located in the ascending limb of the aorta, while in Cases 3, 4 and 5 the pathologic process in the middle coat of the aorta was to be seen throughout the length of this vessel.

The common characteristic of the arterial lesion lay in the presence of patchy or diffuse necroses in the media. For the most part this degenerative process occupied the zone between the middle and outer third of the media though at times it extended inwardly or outwardly into the neighboring zones. These necroses were unaccompanied by an inflammatory reaction, and they were devoid of a fibrosing process in their neighborhood. At the point of rupture there was no lesion of the intima which could serve as a localizing factor, but it was noted that the amount of necrosis in the underlying media was usually greater at this point than elsewhere.

In Cases 1 and 2 where the dissecting aneurysm remained localized to the region of the rupture, the necrotic process was present in patches which partly encircled the aortic wall, and extended to a varying length in a longitudinal direction. These necroses were bland in character and had led to the death of the muscle cells between several of the neighboring layers of elastic fibers. Occasionally the débris of the necrotic tissue remained at the site, but at other times the dissolution of the structure was more complete, leaving only a cleft filled with a colloid-like substance. At times the elastic fibers were spread apart by these small lakes of hyaline material, while at other times the degenerative process had also destroyed these fibers.

The flattened bands of necrosis and the cleftlike spaces in the media formed a procession of lesions encircling the aorta. In each case occasional areas were noted bordering upon the involved zone of the aorta, in which the muscle fibers showed a compensatory hypertrophy. This was more evident in the outer portion close to the adventitia. No direct relation could be established between the distribution of the vasa vasorum and the location of the necrotic process. In one instance the vasa vasorum were found with a moderate amount of endarteritis and a single arteriole showing an organized thrombus. In no instance was there a lesion of the aortic wall resembling syphilis or rheumatic fever.

Beside the degenerative changes in the muscle fibers there were also well-marked changes in the elastic laminæ. Instead of running parallel courses about the circumference of the artery they were irregular in thickness, interrupted in their course, fragmented and often showing brushlike extremities at the termination of the elastic segments. The staining was variable, some fibers showing normal microchemical reactions, others appearing hyalin and jellylike in which the fibrils no longer showed normal staining qualities. The elastic fibers resembled those of old age, at times it was noted that they were very sparse in the vicinity of the vasa vasorum.

The path of the dissecting aneurysm followed the layer in the aorta in which the necroses were most extensive. This in our cases has most commonly been along the outer border of the middle third of the media. Occasionally the path would divert toward the adventitia or again toward the intima. On no occasion did the dissecting process enter the intima proper, and only in the regions where the external rupture of the aneurysm took place did the tear enter the adventitia. The wall of the dissecting aneurysm, made up of an inner and outer lamella of aortic tissue, showed a diffuse or patchy destruction of the media. In 2 cases a granulation tissue developed upon the torn surfaces with some organization of the blood in the aneurysmal sac, otherwise the immediate borders of the cavity were without reaction.

As previously indicated, the muscle fibers suffered more than the elastic fibers, and the extent of the destruction varied considerably. In some instances the aortic wall was not thinned, but the spaces intervening between the neighboring elastic lamellæ were filled with débris and fluid equal to the muscle tissues which had previously occupied the area. In the earliest stages of the degeneration, muscle fibers were found with altered nuclei or with remnants of nuclear material. Subsequently, the area became devoid of nuclear structures, while the cytoplasm of the cells resisted autolysis. These areas became acidophilic. A point worthy of comment is that in this series of cases there was an absence of the granular calcareous deposit which not uncommonly is found in the same zone in elderly people. This latter lesion, which we have previously described, represents a senile medial sclerosis of the aorta, analogous to Moenckeberg's sclerosis of the peripheral vessels. Under these conditions the elastic lamellæ are more closely compacted and thinning of the vessel wall takes place.

No unusual fatty changes were found in the middle coat of the aorta. Small clusters of granular fat were seen in groups of muscle fibers, but these were no more prominent than those found in individuals of this age.

A number of reactions secondary to the development of the dissecting aneurysm were also observed. It was noted that in the cases with extensive dissection of the aorta an edema developed in the intimal tissues and at times when life had been prolonged for some little time after the tear had occurred, a bordering strip of necrosis followed each side of the aneurysmal sac.

Discussion. In order to analyze the conditions in the aortic wall which are associated with spontaneous rupture, we have collected a series of cases from the literature, but have excluded all in which some demonstrable extraneous cause was apparent. Thus we have not included instances of infection and abscess formation in the aorta nor cases of exogenous tuberculous erosion which is at times observed in the thoracic aorta. Furthermore, as there are definite and peculiar changes arising in old age, quite different from the type lesion which is related to the occurrence of the tragedy in the younger individuals, the 42 cases of spontaneous rupture which we have collected from the literature, are limited to those individuals under 40 years of age. In none of these was there any evidence of an external factor, nor could it be shown that the rupture was related to an infectious process. It is of course evident, as we ourselves have encountered in 2 of the cases here reported, that the character of the lesion demonstrable in the aorta in individuals under 40 years may also appear in elderly individuals;

nevertheless, as some confusion may arise as to the actual tissue changes which may be encountered in aortic rupture in elderly individuals, we have omitted these from the present series. Erdheim and Gsell have both shown that the peculiar degenerative changes encountered in the media before middle life may be present in the cases of spontaneous rupture in individuals of advancing years. Cellina, on the other hand, points out that in elderly individuals, destructive changes in the muscle and elastic fibers are of several kinds, and that the specific quality of mucoid degeneration of the musculature is not the sole destructive lesion in the vessel.

The analysis of the cases collected from the literature appears in the following table:

TABLE 1.—RUPTURE OF AORTA (IN INDIVIDUALS UNDER 40 YEARS). Number of cases, 42; males, 28; females, 14.

Ages:			
1 to 10			2
11 to 20			7
21 to 30			20
31 to 40			13
Interval to death:			
Immediate death			6
Hours interval (A few hours to 12 hours)			5
Days interval (1 day to 5 days)			7
Weeks interval (12 days to 5 weeks)			3
Not stated			21
	Present.	Absent.	Not stated.
Associated physical strain	12	26	4
Death sudden	40	1	1
Dissecting aneurysm	17	7	18
Rupture into pericardium	32	7	3
Arteriosclerosis of aorta	10	20	12
Syphilis (determined by Wassermann reaction)	1	13	28
Location of rupture:			
Ascending aorta			33
Arch			6
Thoracic aorta			1
Not stated			2

Spontaneous rupture of the aorta appears to occur twice as often in males as in females; and though it may appear in any decade of life, even in children under 10, it is more common in the later years. No explanation is evident to account for the higher incidence in the reported cases in the third decade over the fourth. Physical strain is a determining cause in a minority of the cases, and in no instance was it the important reason for the development of the peculiar aortic lesion found in these cases.

The onset of the rupture is usually accompanied by severe intrathoracic and radiating pain, while dyspnea and nausea commonly follow. Death does not always take place with the initial tear, as the rupture may penetrate only the inner coats of the arterial wall and not lead to complete rupture. Death may be delayed for a

period of weeks, and even, we believe, not take place as a result of the partial rupture; but the condition may continue to persist as a dissecting aneurysm which may, through granulation tissue, undergo healing. It is our interpretation that every dissecting aneurysm represents a partial rupture of the aorta, and that the conditions underlying the development of dissecting aneurysm are those found in spontaneous rupture of the aorta. This background upon which rupture of the aorta occurs is a peculiar degeneration of the media of the aorta, and is not associated with an antecedent inflammatory process. It is obvious from the evidence in our own cases, as well as from that of the literature, that syphilis plays no part in the production of spontaneous rupture nor in dissecting aneurysm. The very nature of the syphilitic process, with the development of connective-tissue bands in the aorta, precludes the splitting of the aortic wall into lamellæ as seen in both of these lesions.

In each of our 5 cases of spontaneous rupture of the aorta, there was evidence of some degree of dissecting aneurysm, although in 2 of them the condition remained localized to the vicinity of the tear, and might readily have been overlooked. This is particularly true in the younger individuals in whom the dissecting quality of the vessel wall is less pronounced, save at the very margin of the tear where the peculiar degenerative changes in the media are localized.

The greatest frequency of the tear in the aortic arch is determined by the medial degeneration which most often occurs with intensity in this region. With advancing years there is a tendency for the peculiar degenerative changes to become more widely distributed and to occupy a considerable extent of the aorta. We have observed a patchy distribution of this mucoid degeneration in both the thoracic and abdominal aorta, but the most advanced process, associated at times with a bland necrosis of the muscle tissue, is more common in the ascending aorta than in other regions. It is worthy of note that this peculiar destructive lesion of the aortic wall is also to be found in the peripheral arteries of the muscular type. In 1905 Freedman, working in Adami's laboratory, described a cyst of the carotid artery which in structure was similar to the changes which have been so fully described in the aorta by Erdheim, Gsell, Cellina and others. Furthermore, we have observed similar lesions in the renal, coronary and neck arteries in the above cases, in which a complete dissecting aneurysm occupied the aorta.

It is obvious, therefore, that lesions in the intima play no part in the occurrence or localization of the rupture unless, as in rare instances, an atheromatous excavation lies by chance immediately above the lesions in the media. In old age the site of rupture for the production of a dissecting aneurysm may bear a closer relation to the presence of atheromatous ulcers, inasmuch as the latter are not uncommonly associated with senile atrophies of the media which, though differing in their pathogenesis from the mucoid degen-

erations and necroses in younger individuals, give rise to a fragile structure permitting the development of dissecting processes.

There is little direct evidence available indicating the manner in which the medial necrosis makes its appearance. Those who have studied the condition are in agreement that the lesions do not arise through interference with the nutrition by way of the vasa vasorum. None have found thromboses or other occluding processes in these vessels of nutrition, although we have reported the presence in 1 case of an organizing thrombus in several nutrient arteries. In this instance, however, we were unable to relate this circulatory disturbance to the various necroses scattered through the aortic wall. Wiesel believed that the lesions in the media were the result of bacterial toxins, as he had encountered such degenerations in the vascular tissues of children dying of acute infectious diseases. In the absence of other indications, this suggestion was supported by Stoerck and Epstein, and by Gsell. Others contend that not only bacterial toxins, but also certain exogenous poisons (adrenalin, nicotine) and poisonous products of metabolism (renal toxins and liver products) may affect the arterial wall in a manner similar to bacterial toxins. None have been adequately demonstrated to affect the vessel wall in the peculiar manner as related above. Furthermore, the nature of the lesion obtained in animals by the use of adrenalin is not identical with the specific change, as seen in mucoid degeneration. Recently Duff, working in these laboratories, has shown us effects of diphtheria toxin on the media of experimental animals which are very similar to the patchy muscle destruction in man. Admitting that certain bacterial toxins may cause medial degenerations and necroses, it is far from clear how these processes become progressive and appear in their advanced form many years after the infectious process. Nor do the ruptures of the aorta appear only in those individuals who have suffered unusual frequency or severe grades of infectious diseases.

It is possible that certain dietary deficiencies play a part in the degeneration of the vascular musculature and that other superadded factors (toxins) intensify the effect; but it is too early to offer conclusive evidence upon these points. We are, however, of the opinion that the end results are due to a variety of factors and are not dependent upon the effect of one agent alone.

There is need for a thorough study of the degenerative lesions of the media, the recognition of the types and the mode of their development. These lesions are important in the subsequent outcome of clinically recognizable diseases which must not be confused with arteriosclerosis localized in the intima. In the past too little attention has been given to processes affecting the media alone or in which the intima has been involved in a secondary reaction.

Summary. 1. An analysis is given of 5 cases of so-called spontaneous rupture of the aorta.

2. A common underlying process was demonstrated in all cases, consisting of a peculiar noninflammatory degeneration of the media, affecting the muscle and elastic fibers, due to a variety of factors.

3. Similar lesions precede the development of dissecting aneurysms.

4. The peculiar medial degeneration is found, aside from spontaneous rupture or dissecting aneurysm, with increasing frequency with advancing age, either as a diffuse process or in sporadic distribution through the aorta.

5. The lesions have no relation to syphilis.

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THE HYPOTENSIVE ACTION OF POTASSIUM SULPHOCYANATE IN HYPERTENSION.*

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The literature on the pharmacology, the therapeutic effect and the by-effects of the sulphocyanates (thiocyanates, rhodan compounds) has been thoroughly reviewed.[1,2,3] Favorable hypotensive effects have been reported, though a certain number of disagreeable by-effects have been encountered. Fineberg[4] found a large dosage more effective, using 5 grains of the potassium salt for each dose instead of the usual 1½ grains. More recently Ayman[5] and Egloff, Hoyt and O'Hare[6] have reported their inability to use this drug in sufficient dosage to obtain the hypotensive action without producing

* The expense of this study was paid by a grant from the Proctor Fund for the study of chronic disease.

by-effects so unfavorable that the drug had to be given up. While it is true that the effective therapeutic dose of this drug is not far from the toxic dose for some individuals, nevertheless, in a certain proportion of cases the hypotensive action may be obtained without unduly disagreeable symptoms.

Method of Study. It is desirable to have certain criteria by which the presence or absence of a blood pressure lowering effect may be judged since the spontaneous variability of the blood pressure, even in the more advanced stages, is well known, while the favorable response to earnest therapeutic suggestion may be quite marked.[7] In addition to the observations extending over a period of months to years the patients who were the subjects of this study were subjected to special observation, usually under a prescribed régime of diet and rest with or without simple sedatives such as bromids or barbital compounds. Some were given a regular dosage of plain peppermint water, while a few were given potassium sulphocyanate in peppermint water if there had been sufficiently frequent previous examinations during a trial course of some other drug supposed to have a hypotensive action. In all cases the attempt was made to obtain adequate preliminary control in addition to extended previous examinations by other observers.

To avoid the benefits of suggestion and to judge the hypotensive action of potassium sulphocyanate alone, this drug was prescribed in peppermint water in concentrations of 1½ grains and of 5 grains per drachm. During subsequent control periods plain peppermint water was prescribed. These various preparations were prescribed by code and filled by the hospital apothecary. All were given without special suggestion, being alike referred to as for the blood pressure. The more salty taste of the stronger concentration could be recognized and was commented upon by one or two patients. In general, however, the effect of suggestion in these patients was avoided. Courses of 4 to 8 weeks with 1½ grains of the drug 1 to 3 times daily, or 5 grains 1 to 3 times daily alternated with similar periods with plain peppermint water, 1 drachm 1 to 3 times daily. At each visit the patient was examined in the sitting position; the cuff was placed on the left arm (except in a one-armed patient and in one whose arterial circulation in the left arm had been interrupted). A mercury manometer was used; the same observer made the examination. In general the visits were as much alike as possible. Usually ten readings in as many minutes were made. The usual fall in successive readings, especially the later ones, was found in most cases; this is in part due to modification of the circulation below the cuff since changing the apparatus to the other arm will usually find the first pressures similar to the first pressures found with the cuff on the previous arm. However, the changes each time would be the same and it was felt that a possible effect due to relaxation of nervous tension would be obtained.

Material. Expecting that, should potassium sulphocyanate have an hypotensive action, one could obtain alternate rises and falls in the blood pressure of sufficient degree to be clear and definite, this drug was administered to 63 patients with persistent continued arterial hypertension. Twenty-two were discarded because of incomplete study or poor coöperation, and 5 were discarded because of fall in blood pressure apparently due to loss of weight, the use of bromids, or because of marked unaccountable variations in the blood pressure level before using potassium sulphocyanate.

Thirty-five patients remained in whom the therapeutic and toxic effects of potassium sulphocyanate were studied. Fifteen were males and 20 were females. Their ages by decades were as follows: 30 to 39 years inclusive, 4 patients; 40 to 49 years inclusive, 12 patients; 50 to 59 years inclusive, 15 patients; 60 to 69 years inclusive, 4 patients.

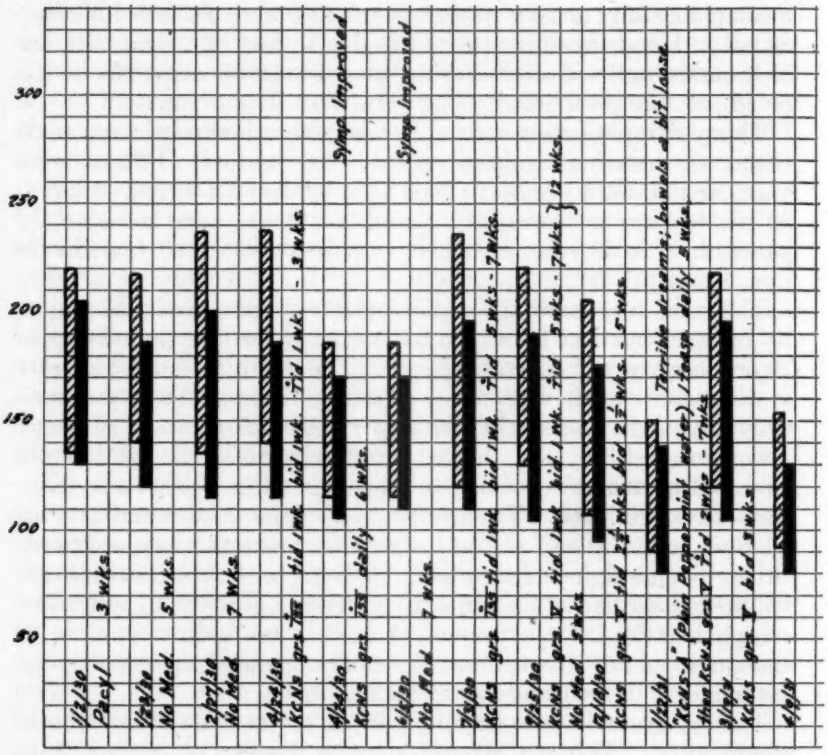
The exact duration of the hypertension was unknown in the majority of cases but was known to have existed for long periods up to 10 or more years in several patients. The majority showed at least some evidence of the late effects of continued arterial hypertension. Only 3 were diagnosed essential hypertension alone and 1 of these, a woman aged 35 years, showed arteriosclerosis of the aortic arch. Five had pure hypertensive heart disease and in 1 other this diagnosis was questioned. Twenty-five had "hypertensive and arteriosclerotic heart disease" and in 1 other this diagnosis was questioned. Other diagnoses included angina pectoris in 5, congestive heart failure and cardiac asthma in 4, hypertensive crises or hypertensive encephalopathy in 3, hypertension of the "malignant type" in 4, and carcinoma of the rectum successfully operated upon and without evidence of recurrence or metastasis in 1.

The eye grounds were examined in 22. Nine showed no definite abnormality. Thirteen showed various degrees of change from mild arteriolar sclerosis to marked hypertensive retinitis with hemorrhages and papilledema. Twenty-eight of these patients were studied fluoroscopically and by means of Roentgen ray plates with the tube at 7 feet. Nineteen of these 28 cases showed cardiac enlargement, 16 especially of the left ventricle. In 2 the enlargement was general and in 1 the shadow was rounded. Tortuosity of the aorta was present in 23 cases. This finding was accompanied by dilatation of the aorta as well in 5. The aorta was dilated without tortuosity in 1. Thus the majority of patients in this series gave evidence of structural changes, the result of or accompanying continued arterial hypertension.

Results. (*a*) *Hypotensive Action.* If, during administration of the drug, the blood pressure of the patient was definitely lower than when the drug was not given, if moreover the blood pressure rose when the drug was omitted and again fell when it was given, the hypotensive action was regarded as certain. Sometimes this cycle

was again repeated. Of the 35 cases studied 7 showed this undoubted hypotensive action. Chart I shows an effect considered certain.

If a similar though not so marked an effect was obtained or if the blood pressure was at first higher without the drug, then lower


300
250
200
150
100
50
Sympt. improved
Sympt. improved
3 wks.
5 wks.
7 wks.
3 wks.
6 wks.
7 wks.
12 wks.
5 wks.
2½ wks.
5 wks.
3 wks.
5 wks.
5 wks.
7 wks.
7 wks.
5 wks.
5 wks.
5

an effect regarded as probable. If the blood pressures fell when on the drug but did not exhibit the subsequent rise without it and another fall with it or if the variations were not as clear as in the probable reactions, the results were held to show possible hypotensive effects, as illustrated in Chart III. There were 13 such patients. Eleven failed to show any hypotensive action. Eleven (31.42 per cent) of this series of 35 patients exhibited either a certain or a probable hypotensive action of potassium sulphocyanate.

(*b*) *Dosage Required.* The dosage was varied considerably according to the ability of the patient to take the drug, but in general two

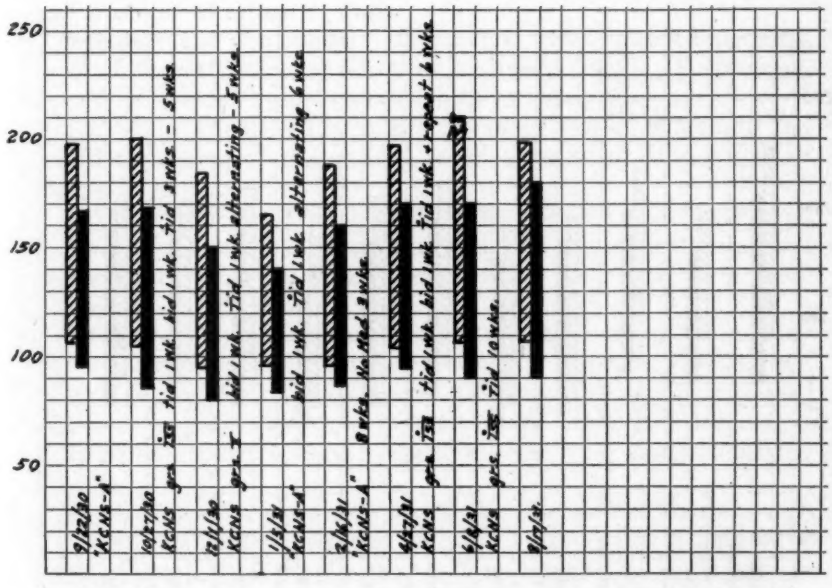


CHART II.—A probable hypotensive effect of potassium sulphocyanate. The result is not as clear as that shown in Chart I. In this case a second fall in the blood pressure under the influence of potassium sulphocyanate was not obtained, though it might have been had larger doses been used. The first fall under its influence, however, seemed to be very definite.

concentrations were employed, 1½ grains per drachm and 5 grains per drachm of peppermint water. These doses were given from 1 to 3 times daily for 4 to 8 or 10 weeks. The weaker concentration only was used in 15 cases while both the weaker and stronger concentrations were used in 20, which included the 7 patients showing the certain effect and the 4 patients showing the probable effect. Only 4 patients in whom the stronger concentration was used failed to show at least a possible hypotensive effect.

(*c*) *By-effects.* In the 35 patients disagreeable by-effects were encountered 9 times and in 2 additional patients symptoms occurred

which may have been due to the drug, in 1 an acneiform rash and in the other a questionable increase in anginal pain and weakness, complaints which were present before the use of the drug. The symptoms definitely related to the drug in the 9 patients were as follows: increase in anginal pain once and onset of anginal pain once; general weakness twice; nightmares once; gastrointestinal symptoms once; nausea and feeling of nervousness once; vertigo with some mental confusion once; and a severe toxic psychosis once. In 6 cases the higher concentration of the drug was used. Weakness in 1 patient and angina pectoris in 2 cases resulted apparently from the smaller dosage.

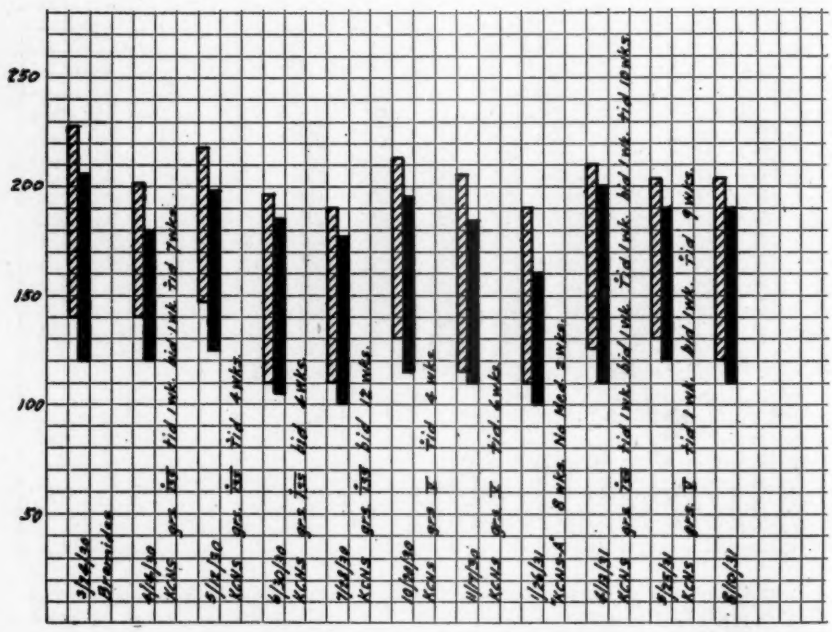


CHART III.—A possible hypotensive effect. There seemed to be a definite hypotensive action exerted by potassium sulphocyanate, though the effect was not as clear-cut as in the group of certain effects represented by Chart I.

Blotchy red measles-like rashes have been noted in 2 patients not in the present series, 1 the patient of a colleague and 1 a patient treated since study of this series was completed. In the first patient the rash appeared a week after taking 5 grains 3 times daily and in the other after a similar time on 1½ grains 3 times daily. Another patient reported to me by a colleague developed an acneiform rash similar to a bromid rash after 2 weeks' treatment.

Unaccountable nervousness with some nausea was complained of by 1 patient while taking 5 grains of the drug 3 times daily. With a similar dosage another experienced terrifying dreams. Two patients

not in this series (1 excluded because of too brief observation and 1 treated since completing this study), experienced acute attacks of excitement; mental confusion and apprehension in 1 lasted ½ hour, in the other continued in a somewhat milder degree for 24 hours. The most marked nervous manifestation amounted to a true psychosis requiring admission to the Boston Psychopathic Hospital. This unfortunate result was accompanied by a fall in systolic pressure from a previous average for several weeks of 200 mm. of mercury systolic to 115 mm. systolic. A good recovery was made, after which the pressure again gradually rose to its former level. The patient volunteered that she felt better than she had for 2 years and was able to return to work.

Summary and Conclusions. Thirty-five well controlled patients, most of them showing the effects of continued arterial hypertension, have been treated by potassium sulphocyanate.

This drug when used in sufficient dosage caused a definite and marked lowering of the arterial blood pressure in 31 per cent of the patients.

Toxic effects are skin rashes, gastrointestinal symptoms and central nervous system symptoms, such as acute apprehension and excitement, which may be severe enough to constitute a toxic psychosis.

Weakness may accompany the use of the drug but is probably not a toxic effect and does not necessarily contraindicate its use. Angina pectoris, in those subject to this symptom, may be increased and in some patients may be induced by the use of this drug.

Toxic effects are reduced to the minimum by carefully controlled dosage.

Limited observation of the use of the drug in combination with a general régime including rest and diet suggests that it may be of value, though these results may not be referred to in accurately appraising the hypotensive action. Generally speaking it may be said that the hypotensive effect is not lasting and that a second or third such effect after the drug is once discontinued is more difficult to obtain.

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HARMFUL EFFECTS OF NITROGLYCERIN.

WITH SPECIAL REFERENCE TO CORONARY THROMBOSIS.

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NITROGLYCERIN is generally considered a drug in no way dangerous to prescribe, and it is usually administered without any particularly careful observation or supervision. However, in the course of recent studies in which therapeutic doses of nitroglycerin were given to 110 patients under direct observation, we observed alarming reactions to the drug in 4 instances. The reactions in the 4 patients were similar in many respects. In each case there was a rapid and marked drop in blood pressure, and the pulse rate was greatly diminished. Severe constitutional symptoms developed in all 4 patients, consisting chiefly of cold perspiration, weakness, restlessness, anxiety, and pallor. Each patient presented a picture of impending collapse. The blood pressure of 2 patients became so low that it could not be recorded, and the pulse could not be felt. The rapid fall in the blood pressure of another patient apparently was checked by the quick administration of epinephrin. Complete heart block developed in 1 case; in another case the course of coronary thrombosis was thought to be unfavorably influenced.

Literature.—Toxic reactions to therapeutic doses of nitroglycerin have received little mention in the literature. The older writers seem to have been more cognizant of these harmful effects of nitroglycerin than modern writers. Shortly after the drug was established as a therapeutic agent by Sobrero[1] in 1847, there appeared several articles pointing out the dangers of the drug. Honert,[2] Field,[3] and Noer[4] reported toxic reactions to therapeutic doses of the drug. In Honert's patient unconsciousness developed; Field, taking the drug himself, was observed to become pulseless; in Noer's patient there was great prostration, cold clammy perspiration, slow and heavy breathing, and a very slow and irregular pulse following the administration of the drug. Loeb,[5] in 1908, reported severe collapse which resulted from as little as $\frac{1}{120}$ grain (0.5 mg.) of nitroglycerin.

Several authors have mentioned contraindications and dangers in the use of nitroglycerin without giving specific evidence or case reports. Cornwall[6] mentioned various contraindications to its use

and simply stated that it should not be given to patients "who have any idiosyncrasy in regard to its actions." Peterson, Haines and Webster[7] stated: "In most of the fatal cases a large amount of the poison was taken but it seems probable that a few drops would prove fatal." According to Sollmann[8] even small doses may cause alarming syncope and cardiac slowing.

Recently White[9] called attention to 2 patients who collapsed with syncopal attacks after taking $\frac{1}{100}$ grain (0.65 mg.) of nitroglycerin. In the recent American literature one is impressed by the fact that there exists, with rare exception, a general disregard for the possible harmful effects of nitroglycerin. Perhaps as a result of this there has developed a rather widespread unrestrained use of the drug in all conditions involving spasm of involuntary muscle.

Since we observed reactions in a relatively high proportion (almost 4 per cent) of our cases following therapeutic doses of nitroglycerin, and because these reactions were of a serious character, we consider the subject of sufficient clinical importance to be worthy of emphasis.

Our 4 patients were women between the ages of 58 and 67 years. In 1 patient the diagnosis of angina pectoris was definite; in all 4 patients there was arterial hypertension. In each patient before giving the drug we made repeated determinations of the blood pressure until a resting level was reached. Therefore, the changes in the blood pressure following the administration of the nitroglycerin may be regarded as due to the effect of the drug. In addition the blood pressure was frequently determined during and after the administration of the nitroglycerin. In 2 of the patients several electrocardiograms were obtained during the reactions.

Case Reports. CASE 1.—A woman, aged 67 years, entered the clinic March 15, 1930, complaining of nervousness, weakness and pains in the joints of her hands. These symptoms had begun 9 months previously following a mild accident when a window fell on her right hand. Since then she had also suffered from vertigo, occasional palpitation of the heart on exertion, moderate shortness of breath on climbing one flight of stairs, loss of energy, and slight swelling of the finger joints of the right hand with severe sharp pain in them.

Physical examination disclosed Heberden's nodes on the fingers of both hands. The heart was not enlarged, its sounds were distant, the rate was 80, and the rhythm was regular. The blood pressure was systolic 190 and diastolic 90. The radial arteries were slightly thickened with some beading. Examination of the ocular fundi showed moderate narrowing of the arterioles. The urine was free of albumin, and contained 30 hyalin casts in 10 low-power fields. The Hinton test for syphilis was doubtful. The patient did not return for 2 months because when blood was drawn for the Hinton test at the first visit she fainted and had been apprehensive about returning. On the second visit the blood pressure was systolic 158, diastolic 78. An orthodiagram showed the heart to be of normal size. An electrocardiogram (Fig. 1) showed sinus rhythm, a rate of 70, a P–R interval of 0.17 second, a Q–R–S interval of 0.07 second, the T wave in Lead 1 erect and low, the T wave in Lead 2 slightly inverted, the T wave in Lead 3 diphasic, and left axis deviation.

Chart I and Fig. 1 show the blood pressure and electrocardiographic changes which occurred during the administration sublingually of a pill containing $\frac{1}{50}$ grain (1.3 mg.) of nitroglycerin. The blood pressure dropped in 10 minutes to an indeterminable point. The pulse became very slow and finally not palpable. Pallor, weakness, a cold clammy sweat, restlessness, anxiety and faintness developed. The patient did not lose consciousness. Epinephrin (0.5 cc. of a 1 to 1000 solution) was given intramuscularly. Five minutes later the blood pressure and pulse still could not be determined. Then the blood pressure rose rapidly; in the next 2 minutes it had reached a level of systolic 154, diastolic 80. During the entire period of observation eight electrocardiograms were taken. These showed, among other things, the development of complete heart block.

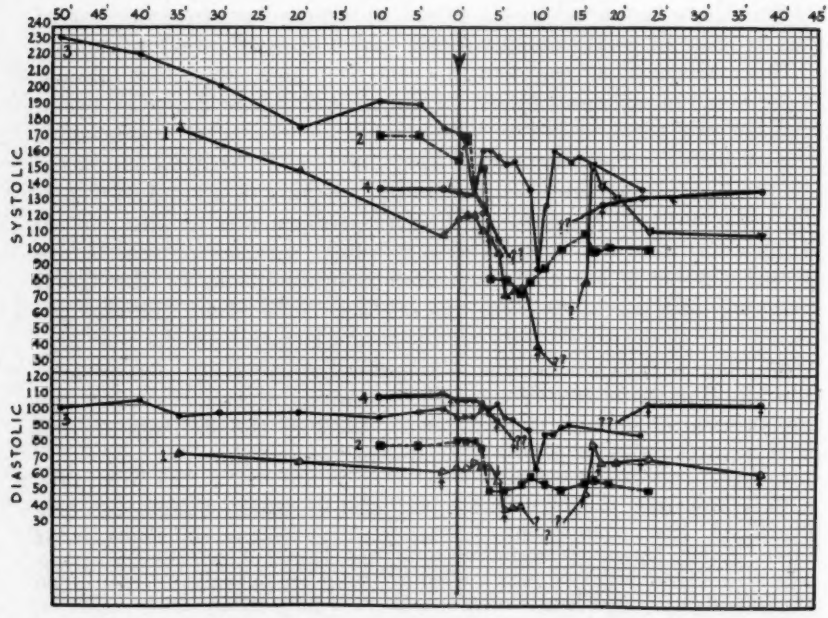


CHART I.—The blood pressure readings of the 4 cases reported; the upper curves represent the systolic, and the lower curves indicate the diastolic pressure. Where the blood pressure became indeterminable, the curve is broken by question marks. To the left of the vertical line at O′ are minutes before, and to the right of this line, minutes after the administration of the nitroglycerin. Small arrows indicate times when electrocardiograms were taken.

CASE 2.—A woman, aged 58 years, had been coming to the clinic for 17 years complaining at various times of pains in the knees, back and thorax, and of light-headedness, shortness of breath, poor appetite, occasional swelling of the legs, occasional headache, faint feeling in the stomach, pain around the heart, sleeping poorly, tiring easily, vomiting, nervousness, numbness in the right ear, and lack of energy.

Physical examination on various occasions disclosed moderate varicosities of the right leg, very slight pitting edema of the ankles, a soft systolic murmur over the apical region of the heart, and slight hypertrophic changes in the terminal joints of the fingers and in both knee joints. During the last 4½ years arterial hypertension had been present. In January, 1927,

the blood pressure was systolic 205, diastolic 110; in January, 1928, it was systolic 175, diastolic 110.

On November 13, 1930, the patient was given $\frac{1}{100}$ grain (0.65 mg.) nitroglycerin (1 drop of freshly opened spirits of nitroglycerin). The effect on the blood pressure is shown in Chart I. Within 3½ minutes the blood pressure dropped from systolic 172, diastolic 84, to systolic 82, diastolic 52. The patient began to feel generally weak, light-headed, restless and nau-

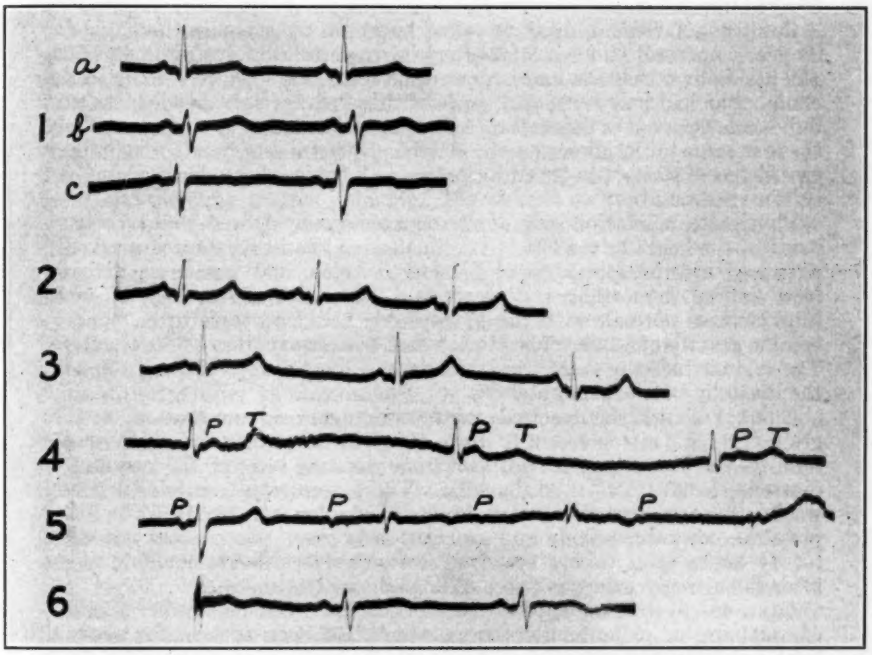


FIG. 1.—Electrocardiogram number 1: *a*, *b*, and *c* are Leads 1, 2, and 3 respectively. This electrocardiogram was taken 2 minutes before $\frac{1}{50}$ grain nitroglycerin was given. . . . Electrocardiogram number 2 shows Lead 1, 5 minutes after $\frac{1}{50}$ grain nitroglycerin; the heart rate has increased from 82 to 95 per minute. . . . Electrocardiogram number 3 shows Lead 1, 6 minutes after the nitroglycerin, rate 66. . . . Electrocardiogram number 4 shows Lead 1, 10 minutes after the drug; nodal rhythm, rate 47. . . . . Electrocardiogram number 5 shows Lead 3, 16 minutes after nitroglycerin, showing complete heart block; the *P* waves are inverted indicating probable retrograde conduction; auricular rate 65, ventricular rate 50; note general diminution in voltage; this is probably not due to position change of the heart associated with respiration, as the breathing at this time was no different than when electrocardiogram number 4 was taken, when no such changes were observed in Lead 3; it is likely that the marked diminution in voltage was associated with the collapse and weak heart action.

Horizontally 1 cm. = 0.35 sec.; vertically 1 cm. = 1.25 millivolt.

seated. She became pale and cool to the touch, and perspired freely. The pulse became very slow and feeble; the rate was 44 a minute. At once 8 minims of epinephrin (1 to 1000) was given subcutaneously, and this dose was repeated in 3 minutes. Twenty-six minutes later the blood pressure still was only systolic 100, diastolic 58, and the patient looked and felt very ill. Sixty-five minutes after the injection of epinephrin the blood pressure had risen only to systolic 136, diastolic 56. The patient has been observed

in the clinic since then up to the present time, and no permanent ill effect of the nitroglycerin has been observed. She has continued to have arterial hypertension.

An electrocardiogram taken one week after the nitroglycerin was given did not show abnormalities. An orthodiagram taken 1 week afterward showed the heart to be of normal size and shape. Study of the ocular fundi, April 13, 1931, showed markedly narrowed arteries and considerable arteriovenous compression. The response to the dilution and concentration tests of renal function was normal.

CASE 3.—A woman, aged 64 years, had been observed in the clinic for 2½ years, and had had essential arteriolar hypertension during this period. She had known that she had hypertension for 3 years before coming to the clinic. She had had occasional spells of tiring easily, light-headedness, and dull headaches, but in general had had comparatively few symptoms. When she first came to the clinic she complained of shortness of breath on climbing two flights of stairs, but this disappeared in a few weeks under the administration of bromids.

Physical examination and a teleroentgenogram showed slight enlargement of the heart to the left. Examination of the fundi showed markedly narrowed arterioles, moderately engorged veins, and numerous old and fresh retinal hemorrhages throughout. The response to tests of renal function was normal, with the kidney able to concentrate urine up to a specific gravity of 1.025. The Hinton and Wassermann tests were negative. The systolic blood pressure varied on many visits between 252 and 150, and the diastolic between 130 and 88.

Chart I shows the reaction to the sublingual administration of 1/50 grain (1.3 mg.) nitroglycerin (2 drops of spirits of nitroglycerin). Within 9 minutes the blood pressure dropped from a resting level of 178 systolic, 98 diastolic, to 90 systolic, 66 diastolic. The patient said she felt tired and weak. She appeared pale and anxious. The pulse rate was 48. The blood pressure, however, quickly and spontaneously rose. The patient felt weak for 1½ hours after taking the drug. An electrocardiogram a few weeks after the nitroglycerin was taken did not show abnormalities.

CASE 4.—A woman, aged 63 years, was first seen September 7, 1931, complaining of pains in the thorax which had been present for about 1 year. She had had a total of about 50 attacks of the same description. The pain was situated under the middle of the sternum over an area about 10 cm. in diameter, and when very intense it was also present in both forearms. The sensation was described "as if something were expanding" in the thorax. It lasted 2 to 3 minutes and then subsided. There was no difficulty in breathing when the pain was present. Following the attacks there were eructations of gas. At no time was there shortness of breath. During the last year the pain had been brought on occasionally by walking up two flights of stairs, but in the 3 days before the patient was first seen it had been induced by the mild exertion of the minor duties of housework. The pain had been more severe during these 3 days, and the patient had been forced to stop immediately when it came on. Two nights previous to examination in the clinic the pain had waked the patient out of a sound sleep. The family history showed that the patient's father had died at the age of 63 of "angina pectoris." A sister had arterial hypertension.

Following the excitement and exertion of undressing for the examination the patient stated that she was having an attack of pain. The blood pressure was then systolic 218, diastolic 140. Eight minutes later the pain had disappeared and the blood pressure was systolic 194, diastolic 128. The important points in the physical examination were as follows: the skin was slightly dry; moderate arteriovenous nicking in the fundus oculi was present; cardiac impulse was felt in the fifth interspace 12 cm. to the left

of the midsternal line, with a powerful impulse over an area the size of three finger tips; the cardiac measurements on percussion were 12 cm. to the left and 5 cm. to the right of the midsternal line; there were no thrills; the heart sounds were of fair quality, with no weakness of the first sound, rate of 95 and regular rhythm; there were no murmurs and no friction rub; the pulse was of good quality; the radial arteries were soft, and edema was not present.

Nitroglycerin in a dose of $\frac{1}{150}$ grain (0.43 mg.) was prescribed for the pain. The next morning the patient stated that she had taken one nitroglycerin pill the night before with moderate relief of the pain. She had not experienced headache, faintness or other discomfort following the nitroglycerin, but she had felt a quivering sensation over the heart. At 9 A.M. the pulse rate was 92, and the blood pressure was systolic 160, diastolic 118. On the same day at 1 P.M., after a half hour's rest reclining, the blood pressure was systolic 136, diastolic 108. The patient felt and looked well. At this time she was given sublingually a nitroglycerin pill containing $\frac{1}{100}$ grain. In 6 minutes the blood pressure had dropped to an indeterminable level, and the pulse was not palpable. The patient became anxious, restless, pale, cold, moist with perspiration, and nauseated. Three subcutaneous injections of epinephrin (0.4 cc. each of a 1 to 1000 solution) were administered over a period of 12 minutes. During these 12 minutes the blood pressure and pulse were unobtainable and the patient appeared to be in a state of collapse. Then the blood pressure gradually rose to its resting level (Chart I). The patient vomited once. A few minutes later she complained of slight pain in both forearms, probably brought on by the epinephrin.[10] This subsided after she lay quietly for a few minutes. The patient was able to return home in a taxi. Some of the electrocardiograms taken during this period are shown in Fig. 2.

The patient was not seen again until 4 days later, at her home. She stated that since the reaction from the nitroglycerin she had felt very weak, and had had inconstant nausea. She had not experienced pain or shortness of breath, but she was barely able to get around her home because of weakness. She looked pale. Her skin was cool and moist. Her pulse was thin and regular, and the rate was 92. The blood pressure was systolic 80, diastolic 70. The heart still had a forceful impulse although the impulse was more easily compressible than when palpated on the first visit to the clinic. There was a marked systolic thrill localized at the apex. A very loud blowing systolic murmur was present at the apex. The measurements of the heart were unchanged. The sounds were of fair quality; the rate was 90 and the rhythm was regular. The aortic second sound was equal in intensity to the pulmonic second sound. There was no pericardial rub. The edge of the liver was not felt. The respirations were shallow and regular, and the rate was 38 a minute. Examination of the lungs was negative. The temperature was 97° F. by mouth, and 98° F. by rectum. The white blood count was 12,300, and the differential count was normal. The specific gravity of the urine was 1.030. The urine contained the slightest possible trace of albumin when tested with heat and acetic acid. Sugar was not present. The patient was at once put to bed and treated for coronary occlusion. She was seen repeatedly during the next few days. The blood pressure remained at the same low level. A state of circulatory collapse continued for 6 days, and death occurred from bronchopneumonia.

Comment. In Case 1, about 10 minutes after the administration of $\frac{1}{50}$ grain (1.3 mg.) of nitroglycerin the blood pressure had dropped to a point at which it could no longer be determined, the pulse could not be felt, and complete heart block developed. We are fortunate in having, in addition to frequent readings of blood

pressure, eight electrocardiographic tracings taken before and during the course of the reaction. The electrocardiograms showed first a slight increase in pulse rate, which is common following nitroglycerin. In succession, sinus bradycardia, atrioventricular nodal rhythm, and finally complete heart block (atrioventricular dissociation) were revealed by the electrocardiograms (Fig. 1). With the return of the blood pressure to a normal level following the administration of epinephrin, the heart block disappeared and normal sinus rhythm was reëstablished. An electrocardiogram taken several months later showed no evidence of heart block. The significance of the slight *T* wave changes following the administration of nitroglycerin is to be considered in a later paper.[11] So far as we know there have been no cases in human beings reported which show such definite intracardiac conduction changes following the administration of nitroglycerin.

In connection with the reaction which the patient in Case 1 exhibited, several factors are to be considered. There was a spontaneous drop in the blood pressure over a resting period of 35 minutes before nitroglycerin was given, from a level of systolic 176, diastolic 74, to systolic 120, diastolic 66. In view of this large drop and the previous variations of the blood pressure as indicated in the case report, it is evident that labile hypertension was present. Whether the lability was in any way related to the unusual response which followed the administration of the nitroglycerin it is difficult to say. It may be mentioned that many of our patients with a similar lability of blood pressure did not show such a response to the drug.

Another factor to be considered as possibly related to the unusual response to nitroglycerin in Case 1 is the type of patient, namely an emotionally unstable woman who had been known to have attacks of syncope in response to excitement. It is hardly likely in this case that the great lowering of blood pressure and the development of bradycardia and heart block were due to excitement on the part of the patient, inasmuch as she had had two previous electrocardiographic studies and was apparently perfectly at ease when the nitroglycerin was administered. This state of emotional relaxation was also indicated by the drop in blood pressure during the 35 minute period of rest prior to the administration of the nitroglycerin. Such drops in blood pressure are common phenomena and usually indicate emotional relaxation in labile arteriolar hypertension.[12] When electrocardiograms were taken several months later under similar conditions, at which time sodium chlorid instead of nitroglycerin was administered sublingually, no change in the electrocardiogram, pulse or blood pressure was observed. This also would make it seem unlikely that excitement attending the administration sublingually of the drug could have been responsible for the reaction. The fact remains that in this case of an emotional patient with labile hypertension a therapeutic dose of nitroglycerin produced an

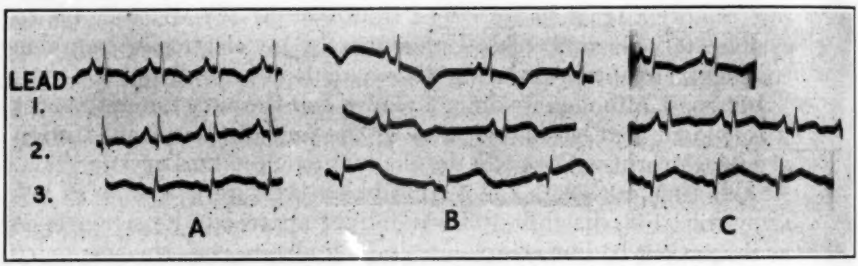
acute, alarming and dangerous reaction. It should be noted, however, that in this case, as in Case 3, a dose of $\frac{1}{50}$ grain (1.3 mg.) of nitroglycerin instead of the more usual dose of $\frac{1}{100}$ grain (0.64 mg.) was given. Whether or not these severe reactions would have been avoided had only $\frac{1}{100}$ grain (0.64 mg.) been given it is impossible to state.

In Cases 2 and 3 the drop in blood pressure was marked, but not beyond determination. Similarly the pulse became slow and weak, but it was always palpable. Subjectively the reactions were similar to the reactions in Case 1 in that there were weakness, vertigo, intense anxiety, restlessness and a sense of approaching unconsciousness. In neither case did unconsciousness supervene. In Case 2 the drop in blood pressure was apparently checked by the administration of epinephrin in two successive doses of 0.5 cc. each of a 1 to 1000 solution. In Case 3 the blood pressure spontaneously rose rapidly after it had dropped from systolic 178, diastolic 98, to systolic 90, diastolic 66. Unfortunately no electrocardiographic tracings were obtained during the reactions in Cases 2 and 3.

In Case 4, although we did not realize it at the outset, in retrospect it is evident that we were dealing at the time of the administration of nitroglycerin with slowly developing, painless cardiac infarction. At this time, although the resting blood pressure level was as low as systolic 138, diastolic 108, we did not appreciate its significance as the patient had no complaints and felt able to perform customary activities. However, the blood pressure the day before the administration of nitroglycerin was systolic 190, diastolic 128. This fact, together with the clinical course following the administration of the nitroglycerin, indicates that at the time the nitroglycerin was administered the cardiac infarction was probably developing. With the administration of $\frac{1}{100}$ grain (0.64 mg.) of nitroglycerin, the blood pressure dropped in 5 minutes from a resting level of systolic 138, diastolic 108, to a point at which it no longer could be determined. At this time the pulse was not palpable. The alarming aspects of the reaction are further indicated in the case report. The question now naturally arises: Did the nitroglycerin contribute to the fatal outcome of the case? Hadfield[13] pointed out that the size of a cardiac infarction is increased when the blood pressure is lowered artificially. Hubble[14] emphasized the danger of using nitroglycerin in coronary thrombosis on the basis of the work of Hadfield and others, and thought that this danger makes it important to distinguish clearly between simple angina pectoris and cardiac infarction. In the American literature, on the other hand, nitroglycerin is considered of such little danger in coronary thrombosis that it is frequently advocated as a means of distinguishing between angina pectoris and cardiac infarction. Levine,[15] White,[9] Eggleston[16] and Gorham,[17] among others, simply stated that nitroglycerin is of no value in coronary thrombosis and indicated its differential diagnostic

value in the latter disease and angina pectoris. The possible dangerous effects are rarely mentioned, and as a result there is in general little or no hesitation in giving nitroglycerin when a patient is suspected of having coronary thrombosis.

In Case 4 the electrocardiogram taken immediately before the administration of nitroglycerin showed evidence of coronary disease. The electrocardiograms taken at the time when the pulse could not be felt and before epinephrin was given showed sinus bradycardia with marked exaggeration of the *T* waves in all leads (Fig. 2). There was no evidence of disturbance of intracardiac conduction. There was, however, definite evidence of increasing cardiac ischemia. In Lead 3, for example, the take-off of the *T* wave becomes distinctly higher while the *S-T* interval in Lead 2 becomes more characteristically "coronary" in type. These changes



Horizontally 1 cm. = 0.35 sec.; vertically 1 cm. = 1.25 millivolt.

FIG. 2.—*A*, Leads 1, 2, and 3, 1 minute before $\frac{1}{100}$ grain nitroglycerin was given under the tongue; *B*, Leads 1, 2, and 3, 7 minutes after the nitroglycerin; note the slowing of the rate, the exaggeration of the *T* waves, the more definite cove-shaped appearance of the *T* wave in Lead 2 and the higher take-off of the *T* wave in Lead 3; *C*, Leads 1, 2, and 3, 38 minutes after the nitroglycerin (three doses of epinephrin, minims 6 each, had been given between *B* and *C*). *T* waves have not completely returned to original appearance although blood pressure had been at starting level for fifteen minutes.

are very similar to those which Feil, Katz, Moore and Scott[18] observed when, after ligation of the left coronary artery in dogs, they lowered the blood pressure artificially by temporarily occluding the inferior vena cava. In their experiments and in Case 1 reported here, it appears that the mere lowering of the blood pressure did not produce myocardial ischemia. It was only when there was some coronary occlusion, as in Case 4, that lowering of the blood pressure produced these ischemic changes. The fact that the patient's condition became suddenly and rapidly worse immediately following the taking of the nitroglycerin indicates causal relationship since such a quick marked effect could hardly have been coincidental. The clinical events, combined with the electrocardiographic changes, indicate that nitroglycerin is distinctly harmful in coronary thrombosis. Other recent clinical experiences tend to confirm this view.[19] The observations of Luten[20] suggest that nitroglycerin, by lowering

the diastolic blood pressure, may even serve as a contributory factor in precipitating coronary thrombosis in any case of coronary sclerosis.*

The lowering of blood pressure, absence of palpable pulse, and extreme faintness almost to the point of unconsciousness may of themselves be of no particular significance. They may represent simply a transient exaggerated reaction to nitroglycerin, the type of reaction that one frequently sees following the administration of amyl nitrite, for example. The fact is significant, however, that following the administration of nitroglycerin heart block developed in 1 case, and a probably harmful effect on the course of cardiac infarction was observed in another. Common to all 4 cases was a definite slowing of the pulse rate as evidence of toxicity.[21]

The mere fact that patients do not complain of unusual symptoms following the taking of the drug is not an indication that they have not experienced a toxic or unusual reaction. For example, when the patient in Case 1 was questioned after the reaction from nitroglycerin was over, she stated that she had been disturbed chiefly by a feeling of faintness, which is not an unusual sensation following the taking of nitrites. The patient in Case 4 complained after the reaction from nitroglycerin only that it seemed a little close in the room and that she simply wanted for air. Had these 2 patients taken the drug at home unsupervised, they would probably have reported to their physician little or no ill effects.

As a result of our experiences we have made it a rule in both hospital and private practice never to give nitroglycerin for the first time to patients without personal supervision, and observation of the blood pressure and pulse. Usually a small initial dose is given ($\frac{1}{200}$ to $\frac{1}{300}$ grain). Epinephrin is kept readily available. When the response to the drug is normal we feel safe in allowing the patient to take the drug at home. In the rare cases† in which toxic reactions do occur, indicating idiosyncrasy to the drug, it is of course not prescribed.

The harmful effects of nitroglycerin may be easily overlooked in coronary thrombosis; for, this is a disease of grave prognosis and the ill effects of therapy are with difficulty separated from the frequent

* P. D. White has recently observed a patient who, when given $\frac{1}{100}$ grain nitroglycerin to relieve the pain of angina pectoris, developed a syncopal attack which came with the relief of pain. When the patient recovered from the syncopal attack in the course of 15 to 20 minutes his pain came back and he went through the typical illness of coronary thrombosis for which he was in the hospital for several weeks. White feels that, while it is possible that the attack of pain for which he gave the patient nitroglycerin was actually the beginning of coronary thrombosis, it is also quite likely that the attack was one of angina pectoris and that the reaction to nitroglycerin favored the production of coronary thrombosis. White suggests using $\frac{1}{200}$ to $\frac{1}{100}$ grain (0.32 to 0.16 mg.) of nitroglycerin as an initial dose. (Personal communication to the authors.)

† P. D. White, who has given nitroglycerin to more than 500 patients with angina pectoris, knows of bad effects only in 2 cases. (Personal communication to the authors.)

spontaneous fatal terminations. It would seem advisable that patients with angina pectoris who are taking nitroglycerin for the relief of pain should be carefully observed, and at the earliest indication of coronary thrombosis administration of the drug should be stopped. When nitroglycerin is given unwittingly in a case which proves to be coronary thrombosis, careful observations should establish further its possible harmful effects.

Summary and Conclusions. 1. Nitroglycerin in therapeutic doses was administered to 110 patients under direct observation. Alarming toxic reactions were observed in 4 cases. In two instances the blood pressure became indeterminable and the pulse could not be palpated. Heart block developed in one of these, and in the other the course of a cardiac infarction was thought to be unfavorably influenced. A record was made of the electrocardiographic changes which occurred during the reactions in these 2 cases. In the other 2 cases there were, as evidence of toxicity, marked slowing of the pulse rate, great drop in blood pressure, and severe constitutional symptoms.

2. Careful supervision of the patient is advised when the first dose of nitroglycerin is administered, in order that those who have an idiosyncrasy to it may be discovered and possible dangerous reactions avoided. A small initial dose ($\frac{1}{200}$ to $\frac{1}{300}$ grain) is advised.

3. The possible harmful effects of nitroglycerin in coronary thrombosis are indicated.

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NEUROBLASTOMA OF THE ADRENAL WITH MULTIPLE METASTASES.

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Neuroblastoma of the adrenal is a rare type of tumor originating in the medulla of the gland, which is a part of the chromaffin system and develops in connection with the sympathetic nervous system. According to Wiesel[1] the termination of embryonal life does not necessarily signify completion of evolution of the medulla of the adrenal, but on the contrary the medulla is almost exclusively a product of postembryonal development and contains neuroblasts up to and even beyond the period of puberty. The comparative rarity of the tumor is indicated by Saphir's[2] report in which it was found to occur once in 3950 autopsies. Although Virchow[3] was the first to mention the possibility of nerve tissue origin of such tumors his opinions were merely conjectural. Marchand,[4] in 1891, was the first to recognize the tumor as originating in the nervous system and was the first to describe malignant tumors derived from fetal sympathetic ganglia. Roussy[5] notes that the ganglion cells of the sympathetic nervous system are analogous to the cells of the central nervous system, having intraprotoplasmic granulations and neurofibrils just like the neurones. He states that sympathomas are often malignant tumors which metastasize throughout the body like cancer. The site of origin may be the suprarenal glands or the paravertebral ganglia, but the early extension of the tumor frequently renders the localization of the primary nodule difficult. The tumors are soft, frequently hemorrhagic and consist histologically of small cells with oval nuclei and very small amount of cytoplasm. The cells are arranged either in a diffuse network or in rosettes on a supporting reticulum consisting of connective tissue and neurofibrillæ. Wollstein,[6] in her very interesting series, notes that although the majority of reported tumors of this type have been found in or grown from the adrenal medulla, they may grow

from embryonal sympathetic cells or sympathicoblasts anywhere in the body. In 1910 Wright[7] used the term "neuroblastoma" and brought about a general acceptance of the belief in the neuroblastic origin of the growth.

Clinically the growth may manifest itself as the type described by Pepper[8] with pronounced visceral and liver metastases or as the Hutchinson[9] type with secondary growths in the long bones, skull, sternum and vertebræ. Frequently postorbital metastases occur and may cause a protrusion of the eyeball and a confusion with chloroma. The tumor of the adrenal is usually encapsulated and does not tend to invade directly the surrounding organs. Extension occurs usually through lymphatics and bloodvessels.

In view of the rarity and the interesting features it is thought worth while to add the following case to the literature on this subject:

Case Abstract.—J. M., a girl, aged 2½ years, was admitted to Sarah Morris Hospital, February 26, 1931, complaining of pain, swelling of the knees and ankles, difficulty in walking, marked pallor, anorexia, abdominal pains and marked night sweats, particularly about the head.

She had appeared to be entirely well until 7 weeks prior to the admission when she began to have pains and swellings in the joints of both legs associated with difficulty in walking, which persisted for the past seven weeks. During the 2 weeks prior to admission a swelling had been noticed on the right side of the face at the angle of the jaw. The mother had noticed a progressive increase in the pallor, considerable dyspnea during the day, as well as occasional abdominal pain. She had loss of appetite with considerable loss in weight.

She was born about 2 weeks prematurely, delivered normally and weighed 5½ pounds at birth. The static development was normal; at 1 year she weighed 21 pounds.

The father and mother are living and well. Another child, 3½ years of age, is in apparent good health. There was no family history of tuberculosis, malignancy or hereditary disease. No history of miscarriages.

On admission the child was very pale, weak and in poor general condition. She was not in pain, but seemed rather distressed and dyspneic. There was a firm, fixed swelling the size of a hickory nut attached to the right lower jaw in front of the ear. There was an ecchymosis on the left upper eyelid, although there was no protrusion of the eyeball. The pupils were equal and reacted to light and accommodation. No abnormalities were noted in the mouth, nose or ears. There was a moderate enlargement of the cervical glands.

The lungs were apparently normal. There was a loud systolic murmur over the aortic and mitral areas and no thrill. The abdomen was markedly distended. The liver extended 4 fingerbreadths below the costal margin. The spleen was not palpable. The superficial veins on the abdomen and thorax were quite distended. The extremities were thin and emaciated.

Blood Examination. February 27, 1931: Hemoglobin, 45 per cent; red blood cells, 1,250,000; white blood cells, 8,000. Differential count: Polymorphonuclears, 31 per cent; lymphocytes, 58 per cent; mononuclears, 5 per cent; myelocytes, 6 per cent.

March 21: Hemoglobin, 40 per cent; red blood cells, 1,300,000; white blood cells, 15,200. Differential: Polymorphonuclears, 43 per cent; lymphocytes, 47 per cent; mononuclears, 6 per cent; myelocytes, 4 per

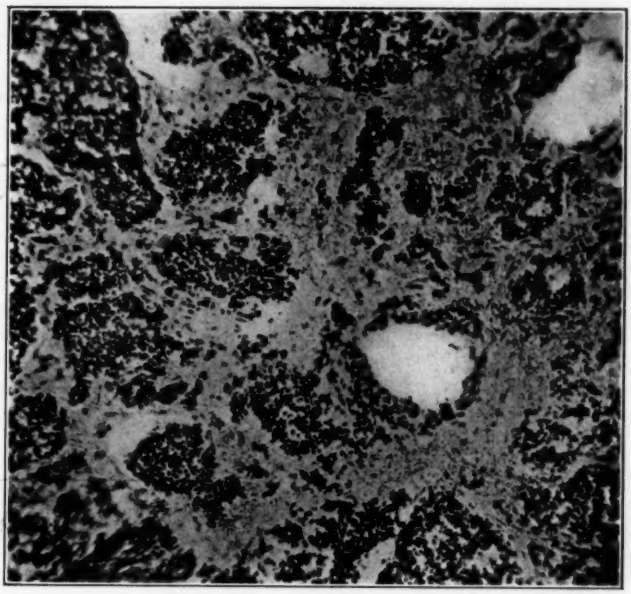

FIG. 1.—Photomicrograph showing "rosettes" of tumor cells.

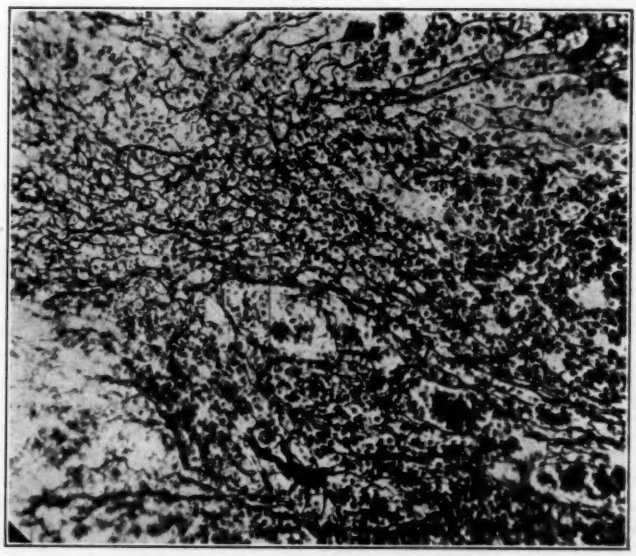

FIG. 2—Pielchowsky stain showing neurofibrillæ.

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cent. The blood Wassermann test was negative. Fragility test: Complete hemolysis, 0.36 per cent NaCl. Beginning hemolysis, 0.42 per cent NaCl. The urine was normal. The test for Bence-Jones albumose was negative.

Roentgen ray examination revealed a pathologic fracture of the right humerus just below the upper epiphysis. There was marked erosion of the left humerus in the same region. There was beginning destruction of the distal end of the left ulna. Practically all of the long bones showed periosteal proliferation and elevation. From the Roentgen ray examination the identity of the pathologic process was not clear. Although there were no characteristic findings a malignant growth was suspected.

The following diagnoses were considered: (1) Osteitis fibrosa cystica with sarcomatous degeneration; (2) sarcoma of the jaw with metastases to other bones and to the liver; (3) malignancy in some abdominal organ with metastases to the liver; (4) chloroma.

Because of the pronounced anemia a transfusion of 200 cc. of citrated blood was given soon after admission. However, there was no favorable response and the child became progressively worse. Soon there was ecchymosis over both eyes. The temperature rose to 105°. The child died a week after admission to the hospital.

Autopsy Abstract. (Dr. O. Saphir.) The body is that of a well-developed, anemic white girl, aged 2½ years. The eyes protrude and there is a hemorrhagic discoloration of the skin over both orbits. There is a firm fixed swelling in the region of angle of the right mandible, anterior to the ear.

The heart shows no abnormalities. There are a few firm areas in the right upper pulmonary lobe, which on cut section are bluish black in color and exhibit a tendency to confluence. The liver is markedly enlarged, reaching into the pelvis, and is studded with many small reddish-blue nodules. The spleen is slightly enlarged and rather firm. The surface shows several reddish nodules similar to those found in the liver.

The right kidney is compressed by a tumor which occupies the place of the right adrenal gland. The genito-urinary tract shows no other abnormalities. The left adrenal is apparently normal. The right adrenal is replaced by an encapsulated tumor which measures 3 by 5 cm. It is soft in consistency and on cut section consists of a dark reddish, in some parts almost black-looking material, which is finely granular in appearance. In the upper portion of the tumor there is seen a large, bright yellow area of necrosis which measures 0.5 by 2 cm. In some portions the capsule is yellowish, resembling the color of a normal cortex of the suprarenal. The tumor has pushed the liver downward and produced a marked depression of the right lobe with pronounced atrophy of this portion of the liver. There are many lymph nodes in the vicinity of the right adrenal which are invaded by the tumor. The aorta in this region is entirely encircled by the tumor nodes. The inferior vena cava in the region of the suprarenal vein shows a thrombus which extends into the suprarenal vein.

The mesenteric nodes and some of the lymph nodes at the mesenteric attachment are invaded by the tumor. The gastrointestinal tract shows no noteworthy changes.

In many portions of the calvarium there is diffuse involvement by the tumor tissue, which occurs in the form of nodules between the calvarium and the dura. Both orbital regions are invaded by the tumor. The brain shows no gross changes.

The osteochondral junction of the ribs shows tumor metastasis into the periosteum. There is a pathologic fracture in the neck of the right humerus. The line of fracture shows a large amount of the reddish-gray tumor tissue.

Microscopically the tumor consists of small round cells with dark staining nuclei. The cells are arranged in groups some of which show necrosis in

the center. The cells surrounding these necrotic areas assume the forms of pseudorosettes. (Fig. 1.) Other areas of the tumor show much necrosis and diffuse hemorrhage in the midst of which only few nuclei were recognizable. Sections stained by Bielschowsky's method reveal many dark fibers throughout the tumor. (Fig. 2.) Sections stained by Hortega's method and by Mallory's glial stain showed glial fibers throughout the tumor. The liver, spleen, lymph nodes and lung were invaded by the same tumor cells.

Pathologic Diagnosis. Primary sympathicoblastoma of the right suprarenal medulla with metastases to the lymph nodes, calvarium, the left humerus, ribs, orbital fat tissue, liver, lungs and spleen. Pathologic fracture of the left humerus.

Summary.—1. A case of neuroblastoma or medulloblastoma of the right suprarenal gland in a girl, aged 2½ years, is reported.

2. There was extensive visceral involvement (Pepper type) combined with numerous metastases in the lymph nodes, calvarium, humerus, ribs, orbital fat tissue, liver, lungs and spleen.

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HYPOGLYCEMIA ASSOCIATED WITH A TUMOR OF THE ISLANDS OF LANGERHANS AND WITH ADRENAL INSUFFICIENCY, RESPECTIVELY.

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The occurrence of hypoglycemia in association with tumors of the islands of Langerhans, or as a result of various endocrine gland disturbances, has lately been well described. Many clinical reports

have appeared in the literature, together with much discussion of the nature of such hypoglycemic conditions. The results of these various observations have seemed sufficiently striking and interrelated to justify the conclusion that the primary factors responsible for the changes in the blood-sugar level are caused either by failure of the liver activities in liberating sugar, or because of overfunction of the pancreas in producing abnormal amounts of insulin. In addition to this it has been pointed out that certain functional disturbances of some of the endocrine glands, such as the thyroid, pituitary and adrenals, may also play a part in causing carbohydrate imbalance in the blood.

Great reductions in the sugar content of the blood have been observed to follow a variety of liver dysfunctions. In all such cases it has been shown that there exists either some faulty mobilization of the sugar, or inadequate storage function of the liver. Such liver dysfunctions are known to arise as a result of certain hepatic diseases, notably in chloroform, phosphorus, hydrazin and arsenic poisoning. Of great interest in this connection is the finding by Nadler and Wolfer[1] of a marked hypoglycemia in association with a widespread carcinoma of the liver.

Of particular interest to us is the part played by the adrenal glands in the causation of hypoglycemia. Unfortunately, the evidence for regarding the adrenals as the chief offenders in causing blood-sugar disturbances is very limited, and in many cases of doubtful significance. We might safely say, that a great deal of our knowledge concerning the rôle played by the adrenals in carbohydrate metabolism is deduced by analogy. Thus, it is well known that the administration of adrenalin will raise the blood sugar and is therefore used to abort hypoglycemic attacks. Also in Addison's disease, where the adrenals have been to a large part destroyed, a condition of hypoglycemia usually develops. Pettersson[2] reports a case of a patient who showed a hypoglycemia of 25 mg. per 100 cc. of blood, and autopsy revealed atrophy of the adrenals and thyroid with enlargement of the pancreas. So too, Anderson[3] reports a case of a tumor of the adrenal gland which produced a fatal hypoglycemia. Just what part the adrenals play in the maintenance of the blood-sugar level is difficult to say, and all the various hypotheses which have been set forth to explain their manner of action are still of a speculative character. Experimental evidence points to the fact, however, that when extracts of these glands are administered to animals, there follows a definite rise in their blood-sugar level.

Hypoglycemic conditions with all the accompanying symptoms of hunger, sweating, nervousness, muscular twitchings, convulsions and coma have also been observed to occur in cases of cyclic vomiting, particularly in children. In many of these cases the blood sugar has been reduced to an exceedingly low level, and the administration

of large amounts of glucose to these patients has promptly relieved the condition. The exact mechanism concerned in bringing about such a hypoglycemic state is still obscure and not definitely determined.

Perhaps the most striking types of hypoglycemia have been noted in individuals in whom a tumor of the islands of Langerhans has been found. The occurrence of hypoglycemia in association with such tumors indicates the possibility of local incitation with increased insulin production. Wilder, Allan, Power and Robertson[4] have shown that such an increased insulin formation could very well result from a carcinoma of the islands of Langerhans. Thalhimer and Murphey[5] have also reported a case of carcinoma of the islands of Langerhans with hyperinsulinism and hypoglycemia. In the case of McClenahan and Norris[6] an adenoma of the islands of the pancreas was found to be the cause of hypoglycemia. Howland, Campbell, Maltby and Robinson[7] are perhaps the first to report a case of an islet tumor of the pancreas where removal resulted in a cure of the hypoglycemia. More recently, Carr, Parker, Groves, Fisher and Larimore[8] and Womack, Gnagi and Graham[9] have reported a case of an adenoma of the islands of Langerhans associated with hypoglycemia. In each of these 2 cases the condition has been diagnosed clinically and surgical removal of the tumor effected a complete cure of the patient.

The occurrence of hypoglycemia in conjunction with an islet cell tumor of the pancreas constitutes a powerful support to the contention expressed by many investigators, that the tumor is the causative agent for the hypoglycemia and the resulting clinical symptoms. It is very surprising to note that, in many of these cases, the tumor found in the pancreas is of unusually small size, and it is rather inconceivable that such a tiny tumor should account for the hyperinsulinism and the resulting hypoglycemia. It seems, then, that other factors must enter to explain the hypoglycemia on the basis of a pure hyperinsulinemia sequent to such a tumor. It is suggested, therefore, that in addition to the quantitative excess of insulin produced by an island tumor, there must be also a qualitative change in the character of such a secretion, insofar as it is much more potent than the normal substance regularly secreted by the normal islands of Langerhans.' It is very difficult to state definitely, however, at this present state of our knowledge what are the abnormal qualities of this insulin or insulin-like substance that is elaborated by an islet tumor, and all the various theories which have been set forth to explain its atypical behavior are merely speculative in nature and not soundly founded.

It is of interest to note in this connection, that the majority of patients who develop attacks of hypoglycemia as a result of an islet-cell tumor are very rarely accurately diagnosed, although the clinical picture which they exhibit is quite unique and typical of hyper-

insulinemia. The neurologic symptoms which these patients present are very often confusing and are therefore misinterpreted. The condition is thus very frequently diagnosed as some disease process of the central nervous system such as epilepsy, syphilis, and others. We are inclined to believe that the infrequency with which these cases are reported is due not so much to their rarity, but rather to the inaccurate diagnosis that is being made. We might also add, that rather little attention has hitherto been paid to this phase of the problem, although we feel that the condition is sufficiently frequent to arouse greater interest.

During the last year 2 cases of hypoglycemia have come to our attention at the Missouri Baptist Hospital.

Case Abstracts. CASE 1.—This case has already been reported by Smith and Seibel;[10] it is Case 4 of their paper. Briefly summarized, this case concerns an elderly white man who entered the hospital because of symptoms of vomiting and abdominal pains. He was operated upon for intestinal obstruction but at operation no obstruction was found; instead, the gall bladder was found filled with stones. The patient died 48 hours after the operation and at autopsy, performed immediately after death, a tumor of the islands of Langerhans was incidentally discovered. Dr. Bensley was able to demonstrate beta granules in these tumor cells by his special technique, but unfortunately these slides have not been preserved. Additional history obtained from the family following the discovery of the pancreatic tumor revealed the fact that the patient was subject to frequent attacks of amnesia and that he consumed unusually large amounts of sugar and sweetened food. There were also periods in which he seemed mentally confused and said strange things, and that such attacks were almost always relieved when fed with sweet food. Because of the above symptoms the family considered the patient as mentally deficient. Although no blood-sugar determinations were made in this patient, yet we felt quite confident, chiefly because of the typical clinical symptoms which he presented, that we were dealing here with a case of hypoglycemia caused by the pancreatic tumor. Furthermore, the cytologic studies made of this tumor revealed changes that were identical with those described in other cases, and in which the patients have been shown to suffer from hypoglycemia.

The second case is of particular interest because it differs from all other cases heretofore reported in the literature insofar as the primary cause of the hypoglycemia was an unusual lesion in the adrenals. This case will therefore be reported in some detail.

CASE 2.—C. S., a white male, aged 20 years, was admitted to the Missouri Baptist Hospital on July 11, 1931, in a state of stupor and semicoma. The history obtained from the family stated that he was apparently well until 2 months prior to his admission to the hospital. At that time the family first began to note in him a change in personality; he became despondent and melancholic and would not eat for several days at a time. He was married and his wife was pregnant; as a result of the general economic depression he was unemployed. The family therefore attributed his psychic state to the above adverse circumstances, and no particular attention was paid to his peculiar reactions. His general condition, however, became gradually worse and he began losing weight and complained of frequent

headaches. It was also noted at that time that he was consuming excessive amounts of sugar and sweetened food and that the latter was out of proportion to his normal dietary intake. The patient claimed that he felt considerably better after eating sweets and was also more alert. Because of the progressive loss of weight and increased melancholia, the patient was sent to the country where he could rest. He felt somewhat better during the first day of his stay there, but on the following day he became very sick at his stomach and later lapsed into coma. He was then brought back to town and admitted to the hospital for observation.

On admission to the hospital the patient was stuporous and could be aroused only with difficulty. On physical examination nothing abnormal was found excepting that his right arm showed spastic contraction and was held in a position of external rotation. Within a very short period after entry to the hospital, the stupor deepened and the patient finally lapsed into complete coma. While in coma he was completely relaxed and the spasticity of the right arm had entirely disappeared.

Because of the very typical history which the patient presented, the condition was diagnosed at once as hypoglycemia, probably due to a tumor of the islands of Langerhans. A blood-sugar determination made of the patient shortly after his admission to the hospital showed a hypoglycemia of 25 mg. per 100 cc. of blood. Treatment was instituted immediately and large amounts of glucose were given intravenously. It was noted that in the course of the administration of the glucose the patient rallied, he began to regain consciousness and recognize the people that were standing around him. He became comatose again when the glucose was discontinued. The beneficial effects of the glucose upon the patient added support to our assumption that we were dealing with a case of hypoglycemia. This was corroborated by several blood-sugar determinations, all of which showed a very marked reduction in blood sugar. The glycemia continued at a very low level in spite of the constant administration of intravenous glucose. The patient finally lapsed into complete coma and failed to regain consciousness until his death, 48 hours later. Very shortly before death the blood sugar rose to 70 mg. per 100 cc. of blood.

An autopsy was performed within an hour after death. Our main attention at the time of autopsy was directed to the pancreas, since we felt quite certain that we were most probably dealing here with a case of hyperinsulinemia caused by a tumor of the islands of Langerhans. Examination of the pancreas disclosed a circumscribed and well defined nodule situated over the anterior surface and tail-end portion of the pancreas. This nodule was sharply demarcated from the surrounding pancreatic tissue. It measured about 5 mm. in diameter, was slightly raised from the surface and had a grayish discolored appearance. On cut section it appeared to extend for a distance of about 3 mm. into the depth of the pancreas. The cut surface of this nodule did not seem to have the same gross characteristics as was noted in the tumor nodule of our first case, but because of its striking differentiation and the absence of all other gross changes in the pancreas, it was anatomically diagnosed as an adenoma of the island tissue. The peripancreatic lymph nodes were somewhat larger and more prominent than normal.

The anatomic examination of all the other organs in the body failed to reveal any gross lesion, and these require therefore no further comment.

The microscopic examination of the nodule recovered from the pancreas disclosed rather unexpected findings. Instead of the suspected tumor of the islands of Langerhans, this nodule was found to consist of a localized area of chronic inflammation. There was not the slightest evidence of any neoplasm being present. In this inflammatory zone there were found isolated, but rather normal islands of Langerhans together with old remnants

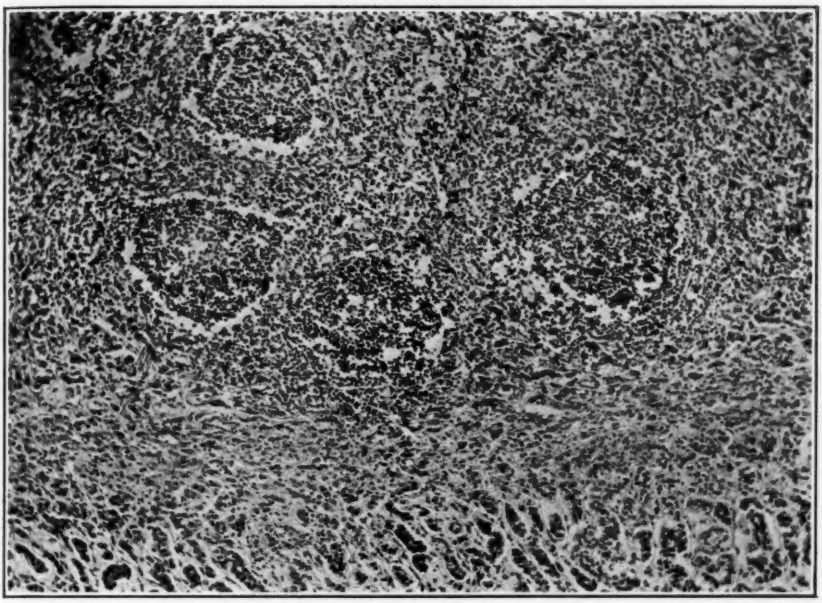

FIG. 1.—Case 2. Photomicrograph showing the lesion in the adrenal. The cortex is of normal appearance, while the medulla is replaced by lymphoid tissue, the latter consisting of lymph follicles and scattered lymphocytes. (× 90.)

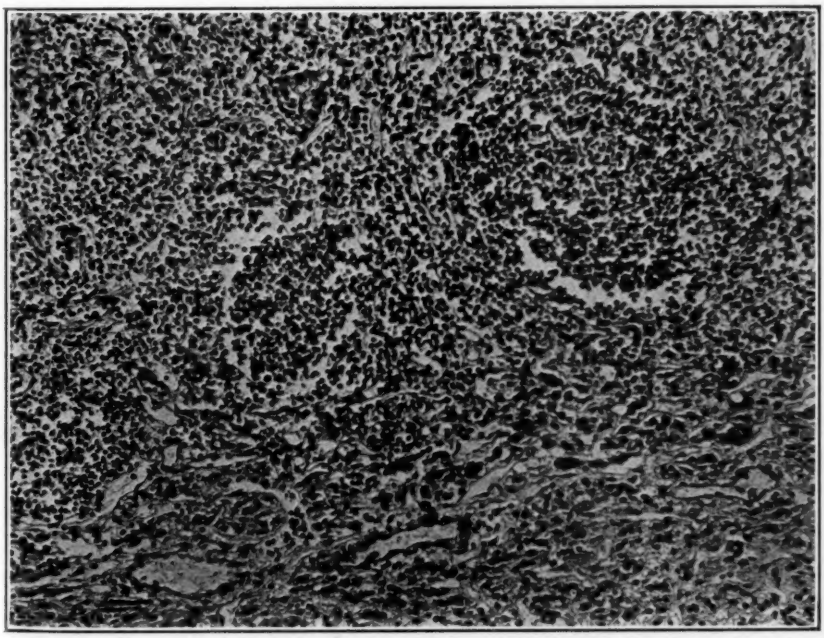

FIG. 2.—Same as Fig. 1 but a higher magnification. (× 150.)

of gland and duct tissue. The stroma consisted here of diffuse fibroblastic proliferation with abundant lymphocytic and other inflammatory cell infiltration. Other portions of the pancreas showed similar inflammatory changes but to a very much less marked degree. The failure to identify this nodule as an adenoma of the island tissue prompted us to search the rest of the pancreas for any possible growth which might have been overlooked at the time of autopsy. The entire pancreas was therefore cut into very thin sections and every suspicious area was examined microscopically. No evidence of any tumor growth could be found in the entire pancreas.

Microscopic examination of the various other organs did not show anything abnormal excepting for certain unusual changes in the adrenals to be described below. The changes noted in these glands were identically the same in each organ and require therefore no separate description. The cortex of the adrenals was destroyed in places, while in others it still maintained its normal architecture and cell outline. The medulla, however, was entirely replaced by lymphoid tissue which was arranged in the form of distinct nests of lymphocytes surrounding a central collection of reticuloendothelial cells. These nestlike structures had all the histologic appearances of lymph follicles, except for the fact that there was no well defined germinal center as is commonly observed in typically constructed lymph follicles. In the spaces between the various lymphocytic nests there was found a diffuse infiltration of lymphocytes and occasional giant cells. These giant cells were regarded as foreign-body cells and not associated with any tuberculous lesion. In addition to the lymphocytes and giant cells, there were also noted scattered in the medulla old remnants of desquamated medullary tissue. No evidence of any normal medullary tissue could be distinguished anywhere in the various sections studied. (Figs. 1 and 2.)

The replacement of the medullary portion of the adrenals by lymphoid tissue was so generalized that, in all probability, no adrenalin was secreted by these organs. We are still at a loss to account for the very extensive substitution of the adrenal medulla by lymphoid tissue. We are inclined to believe, however, that the replacement of the medulla by lymphoid tissue was responsible for the hypoglycemia and for the cause of death of the patient.

Discussion. If we accept as an established fact that marked hypoglycemia may in itself be fatal, it becomes very probable that the hypoglycemia is the principal cause of death, independent of whether it is due to hyperinsulinism resulting from a tumor of the islands of Langerhans, or due to an impaired function of the adrenals because of pathologic changes in these organs. The symptoms observed in our 2 patients were characteristic of hypoglycemia and showed the same general type and degree as those seen associated with fatal cases of hyperinsulinism. Everyone is familiar with the usual symptoms of hypoglycemia that occur in individuals receiving an overdose of insulin, as in the course of treatment in diabetes. All these symptoms were rather typically expressed in our 2 patients and suggested that we were dealing in each case with a similar pathologic process causing a disturbance in the normal balance of the blood sugar.

The various activities taking place in the body during the process of carbohydrate metabolism are very complex, for we have to deal

here not with a simple chemical change, but rather with a complicated mechanism which involves the activities of the various endocrine glands in the body. We are particularly concerned in this paper with the specific effects which the secretions derived from the cells of the islands of Langerhans and of the adrenals have on the metabolism of sugars. Pathologic changes in any of these glands of internal secretion may lead to a fatal hypoglycemia, although the mechanism of their respective actions in inducing such a condition is different in each case.

The hypoglycemia that is found in association with tumors of the islands of Langerhans can best be explained on the basis of increased as well as perverted insulin production. Our knowledge concerning the effects of insulin on sugar metabolism has gained rapid momentum ever since Banting and Best first discovered this substance. As a result of these various experiences we are able to diagnose quite accurately an attack of insulin shock, the symptomatology of which is here briefly recapitulated. It consists of sweating, nervousness, muscular twitchings, convulsions, coma and death. Such a symptom complex is also observed in individuals who have a tumor of the islands of Langerhans. This starts us therefore upon a line of thought which leads to a significant conclusion, namely, that a diagnosis of an island tumor could be very readily made in the presence of such symptoms as have been just described. The typical category of a hypoglycemic attack represents as a rule no unusual diagnostic difficulties, provided of course one keeps in mind the fact that the disease is far from being uncommon. Yet, it is very surprising to find only a very small percentage of these cases being accurately diagnosed, even by the most skillful and painstaking physician. The chief difficulty in making a correct diagnosis is usually due to the very close similarities existing between this disease and an allied number of neurologic disturbances. For this reason we find that many of these patients are referred to the neurologist for diagnosis. The symptoms which these patients present, however, are so unique that it is hardly conceivable they should be overlooked.

Reference has already been made to the exceedingly small size tumor of the pancreas which is held responsible for the hypoglycemia. The histologic studies made of these types of tumors justifies the assumption that they arise from the cells composing the islands of Langerhans. These tumor cells are found to have staining properties very similar to those known to occur in the normal beta cells of the insular portion of the pancreas. These cells are also apparently capable of elaborating insulin or an insulin-like substance, as judged from the body reaction in their presence. We feel, however, that the character of this secretion is somewhat different from the normal insulin, particularly insofar as it is much more potent. Such a conclusion is justifiable, we believe, if we consider the

extreme degree of hypoglycemia that may occur as a result of such an unusually small size tumor.

Of much interest to us is the part played by the adrenal glands in carbohydrate metabolism. This phase of the problem is intricate and still obscure. Clinical data as well as experimental findings point to the fact that one of the functions of adrenalin is to render sugar available for body use. The manner by which it brings this about is not definitely determined, although it is generally believed that it does so by setting sugar free from its normal depots in the liver. It appears then that in cases where this secretion is diminished or entirely lacking to the organism, the blood sugar is correspondingly reduced. It is also felt that the rôle which the adrenals play in the sugar economy of the body is of vital importance to the organism, so much so that complete absence of their secretion may lead to a fatal hypoglycemia. This phase of the problem is very well illustrated in our second case described above. We have noted in this patient all the clinical symptoms of hypoglycemia and the chemical changes were equally significant of a most marked reduction in blood sugar. Postmortem examination and cytologic studies made of the various organs of this patient revealed changes that were entirely confined to the adrenals, while all the other organs, particularly those concerned with carbohydrate metabolism, showed no evidence of any pathologic abnormality. In view of these findings we are justified in associating the hypoglycemia with the lesions in the adrenals. Similar observations were made by other investigators who reported all degrees of blood-sugar disturbances caused primarily by some adrenal disease.

The chief pathologic lesion in the adrenals of the case under discussion was located in the medulla, whereas all other parts of the glands escaped any appreciable damage. It will be remembered, however, that the adrenal medulla is primarily concerned with the formation of adrenalin, and that the latter is the sole product of these glands which influences the metabolism of sugar. It becomes evident, therefore, that in the absence of all medullary tissue no adrenalin will be formed to be available for body use. The resulting effects on carbohydrate metabolism then become quite obvious.

The pathologic changes described in the adrenals of our second case are very interesting. These changes, as will be remembered, consisted in total replacement of the medulla by dense collections of lymphocytes, many of which were arranged in groups around centrally placed reticuloendothelial cells, and gave the appearance of lymph follicle formation (see illustrations). These follicles were sharply demarcated from the surrounding stroma. They did not however, have a well defined germinal center as typically constructed lymph follicles are known to have. In the stroma between the various lymph follicles there was found scattered débris of preëxisting medullary tissue, together with numerous lymphocytes and

occasional giant cells. The exact significance of these lymphocytic collections is not very well understood and we cannot offer any plausible explanation for their widespread distribution in the adrenal medulla. A careful review of the literature has failed to reveal similar instances of hypoglycemia that arose primarily as a result of substitution of the adrenal medulla by lymphoid tissue. It may be theoretically assumed that the lymphoid changes in the adrenals represent a local manifestation of lymphoid dyscrasia, perhaps of some constitutional nature. Such assumptions, however, are conjectural and as such have not special merit. We therefore do not choose to interpret the pathogenesis of this peculiar case and simply content ourselves with reporting it. We are interested in the changes in the medulla at present only from the standpoint of their marked deleterious effects in bringing about a fatal hypoglycemia as described.

From the foregoing discussion it will be evident, we are sure, that several factors may come into play in causing blood-sugar disturbances. Of these the secretions derived from tumors of the islands of Langerhans and the sequelæ of depressed functional powers of the adrenals have been shown to account for some cases of hypoglycemia. A general analysis of the clinical symptoms and of the chemical changes in the blood in these two types of cases shows them to be identical. It therefore becomes a very puzzling problem when one seeks to establish the anatomic seat of the lesion in such patients. Very often it may be a life-saving matter to the patient if the anatomic lesion responsible for the hypoglycemia could be accurately established. As has already been shown, a curative result could be expected in cases where the hypoglycemia is caused by an accessible tumor in the pancreas. With the above facts in mind it is the authors' opinion that surgical intervention should be contemplated whenever a diagnosis of an insular tumor of the pancreas has been definitely made. It is quite obvious that such measures of treatment are entirely out of the question when the cause of the hypoglycemia is due to extensive involvement of the adrenals. Unfortunately, there is no specific test which may be employed in order to differentiate between these two lesions, for both a tumor of the island tissue of the pancreas as well as pathologic conditions of the adrenals may give rise to all degrees of blood-sugar disturbances. Both types of cases also respond equally well to glucose. It is possible, however, that in cases where the adrenals are at fault, other significant clinical and laboratory facts may be found which would shed more light and serve to establish a more definite relationship between the disease process in the adrenals and the accompanying hypoglycemia. In the light of such experiences it becomes obvious that we must always take into consideration all the various causes of the existing hypoglycemia before rendering an anatomic diagnosis.

Summary. 1. The various phases of hypoglycemia are discussed. Two cases of hypoglycemia are reported, one of which (previously published) was caused by a tumor of the islands of Langerhans, while the other was due to adrenal insufficiency.

2. The changes in the adrenals in the second case consisted in complete substitution of the medullary portion by lymphoid tissue. These changes were believed to account for the hypoglycemia in this patient.

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HUMAN PANCREATIC SECRETION STUDIED FROM A CASE OF PANCREATIC CYST WITH FISTULA.

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The opportunity of studying the human pancreatic secretion as it is discharged directly from the pancreas, before it has entered the duodenum, is extremely rare. A survey of the literature reveals a scant knowledge of the enzymatic nature of the secretion. The following case afforded the opportunity to examine a relatively pure pancreatic fluid. The results of some of our investigations on the enzymatic nature of the external pancreatic secretion are presented.

Case Reports. Case 1.—*History.* The patient, N. F., a native letter-carrier, aged 34 years, was admitted on April 5, 1930, to the Mount Sinai Hospital, on the surgical service of Dr. A. A. Berg. Eight years before he began to suffer from abdominal symptoms. At that time he was seized

with attacks of cramplike pains in the abdomen, not localized, and associated with vomiting. These seizures occurred as a rule a half hour after meals and were unrelieved by food. For 4½ years, despite medicinal and dietary treatment, the pain and vomiting persisted. During this time his appendix was removed, without relief of his symptoms. Roentgenographic examination of the gastrointestinal tract revealed evidences of a diseased gall bladder. The patient was then put on a low fat diet, and was practically free from his symptoms for the next 3½ years. Five months before admission he had a sudden attack of severe abdominal pain which lasted 1 week. At this time the gall bladder could not be visualized by the dye test. Three months later there was a recurrence of vomiting. This became progressively worse so that, in the week prior to his admission, every meal was followed by emesis. Pain was no longer present. Food particles in the vomitus represented material eaten at the preceding meal. There was no melena, no acholic stools, no jaundice. For the 5 months prior to admission there had been anorexia and marked constipation, with a loss of 35 pounds during this time.

A gastrointestinal examination with the aid of a barium meal was made by Dr. S. J. Goldfarb.* This showed that the normal acute angle at the junction of the first and second portions of the duodenum was changed to almost a semicircular form, indicating a separation of the first and second duodenal segments by an enlargement of the head of the pancreas. In view of the history of previous gall bladder disease, an acute attack of abdominal pain with subsequent vomiting and the Roentgen findings, a diagnosis was made of a pseudocyst of the head of the pancreas causing obstruction of the pylorus and duodenum by pressure.

Physical Examination. The patient was a moderately well-developed young man, showing evidences of considerable loss of weight. Physical examination of the internal organs was essentially negative except for the following findings: There was a large mass palpable in the right upper quadrant of the abdomen, non-tender and descending with respiration. It felt cystic and was approximately 3 inches in diameter. A succussion splash could be elicited in the left upper quadrant, presumably originating in the stomach. The stomach outline could not be definitely determined. The temperature was 99.8°F., the pulse 110 and the respiratory rate 20.

The laboratory findings included: Hemoglobin, 104 per cent; white blood cells, 9200. Differential count: polymorphonuclears, 55 per cent; lymphocytes, 42 per cent; mononuclears, 3 per cent. The blood Wassermann test was negative. Blood analyses showed: Urea nitrogen, 21 mg. per 100 cc.; sugar, 95 mg. per 100 cc.; cholesterol, 180 mg. per 100 cc.; chlorid, 678 mg. per 100 cc.

The urine was clear, alkaline to litmus and had a specific gravity of 1.018; it showed a trace of albumin, no sugar, and only triple phosphates present in the sediment.

The stomach was aspirated, and 8 ounces of coffee-ground fluid obtained, giving a positive guaiac reaction for blood.

Laparotomy Findings. In view of the complete nature of the obstruction, operative relief was urgently indicated. Laparotomy was performed by Dr. A. A. Berg on April 12, 1930. On opening the peritoneal cavity, a large cystic mass could be felt in the retroperitoneal tissues in the upper portion of the abdomen just to the right of the midline, probably arising from the pancreas. Stones were felt in the gall bladder. Aspiration of the mass yielded 175 cc. of dark, slightly viscid liquid material. An approach was made through the inferior aspect of the transverse mesocolon and the cystic mass incised. There was found a cyst with a thickened

* Dr. S. J. Goldfarb will shortly report this case from the roentgenologic point of view.

and indurated wall, from which could be scraped a blackish material. The cavity of the cyst extended downward toward the pancreas and seemed to be intimately connected with it. A large rubber tube was placed in the cyst cavity and sutured by means of chromic catgut to the cyst wall. The parietal peritoneum of the left margin of the incision was then sutured to the wall of the cyst cavity by means of chromic sutures and the abdomen then closed in layers.

Course. In the week after operation the patient drained through the tube in the cyst 32 ounces of thick, brownish fluid. Several days later the patient began to drain large amounts of an opalescent, cloudy fluid, alkaline in reaction with a peculiar disagreeable odor. This was found to contain large amounts of pancreatic enzymes. As much of this fluid as could be swallowed was fed back to the patient. Despite its unpleasant odor, as much as 33 ounces of this material was taken daily by the patient. The fluid was collected under strictly hygienic precautions and did not prove distasteful to the patient. Drainage through the tube continued for 59 days after the operation. It gradually diminished in quantity and finally ceased entirely. The tube was then removed and the tract permitted to fill in by granulation tissue.

The postoperative blood chemical findings were always normal. There was no evidence of acidosis, alkalosis or disturbance in the carbohydrate metabolism except for one period, mentioned later on, when the patient was kept on a pure carbohydrate diet. Shortly after operation the patient began to develop a voracious appetite, so that he had to be fed almost hourly, with a daily intake of 5000 to 6000 calories. The diet was well-balanced. The stools were not fatty and contained only rare undigested meat fibers. Defecation occurred with customary frequency. There was no diarrhea. The patient felt well, gained weight rapidly and was discharged, asymptomatic, 67 days after the operation. Four months later he was perfectly well, had been free from symptoms on a low fat diet and had gained about 30 pounds. He felt normal in every respect.

In view of the opportunity offered of collecting presumably pure pancreatic juice, some investigations of the pancreatic secretion were undertaken. The material studied consisted of fluid drained through the tube inserted into the cyst cavity at operation and caught in a glass container. The secretion was kept on ice from the time collected until it was analyzed, generally on the next day. A Rehfuss tube was passed into the duodenum on two occasions after operation and both times pancreatic ferments were obtained, proving that some pancreatic secretion was entering the duodenum.

Pathologic Anatomy. The portion of the cyst wall removed at operation consisted of pancreatic tissue with areas of necrosis, chronic inflammation and fibrosis. The fluid aspirated from the cyst contained only débris; no cellular sediment was present.

Clinical Summary. Five months before admission the patient suffered from severe abdominal pain for 1 week. Thereafter vomiting, which had occurred rarely in the previous 3 years, became increasingly frequent up to the time of admission. The period of 1 week's pain probably represents the time when the patient was suffering from an attack of acute pancreatic fat necrosis with resulting destruction of pancreatic tissue and the formation of a pseudocyst, *i. e.*, one not resulting from the retention of secretion after blocking of a duct. This cyst grew steadily larger, causing progressive obstruction of the alimentary canal by external pressure on the pylorus and duodenum. By the operative drainage of the cyst the

pressure was relieved and the vomiting ceased. Postoperatively there was discharge of pancreatic secretion into the duodenum (pancreatic enzymes were found in the duodenum by duodenal bucket) and from the tube inserted into the cyst cavity. The

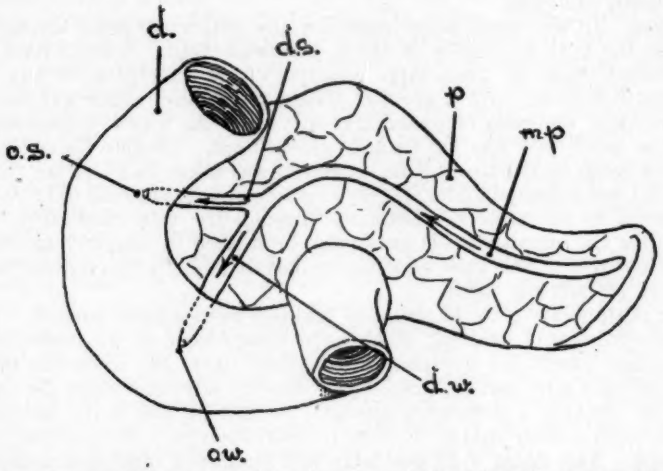

FIG. 1.—Schematic sketch showing a frequent relationship of the pancreatic ducts, modified after Schmieden and Sebening. *d*, duodenum; *p*, pancreas; *mp*, main pancreatic duct; *dw*, duct of Wirsung; *ds*, duct of Santorini; *ow*, opening of duct of Wirsung into duodenum (papilla Vateri); *os*, opening of duct of Santorini into duodenum.

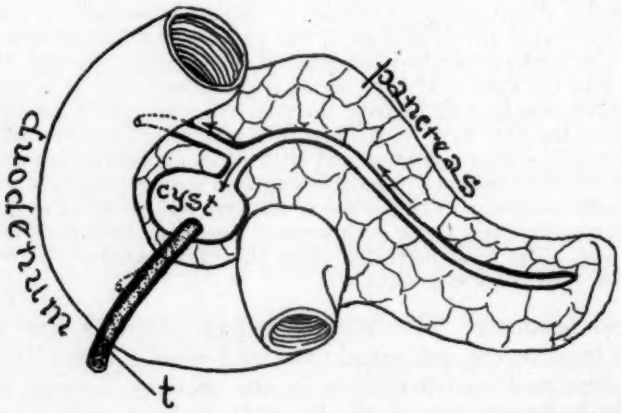

FIG. 2.—Status of flow of pancreatic secretion after operation, indicating presumed common communication of drainage tube and duct of Wirsung with cyst cavity. *t*, drainage tube inserted into cyst cavity.

external drainage gradually decreased and finally ceased 59 days after operation. Opie (1903), Schmieder and Schering (1927) and others have demonstrated that there is frequently an anastomosis between the ducts of Santorini, Wirsung and that draining the

main portion of the pancreas. This relationship is schematically presented in Fig. 1. Fig. 2 represents our conception of the pathologic changes present in our case, indicating the communication between the cyst cavity and one of the outlet ducts of the pancreas. Because of the presence of pancreatic ferments in the duodenum, it is presumed that there was another outlet duct discharging into the duodenum and not into the cyst. In view of the large amount of the fistula drainage, it is probable that the major duct (Wirsung) communicated with the cyst. It is our view that as healing progressed there was gradual obliteration of the cyst cavity with consequent closure of the communication between cyst and duct. The other duct (Santorini) probably assumed the rôle of draining that portion of the pancreas previously drained by the duct of

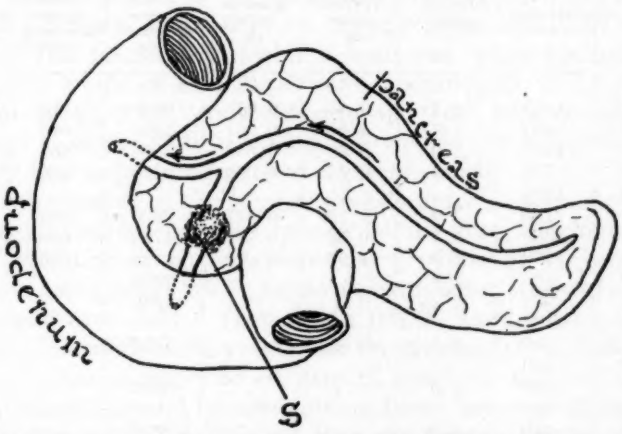

FIG. 3.—Status of flow of pancreatic secretion after cessation of drainage through tube. *s*, scar at seat of obliterated cyst cavity. NOTE.—Communication between cyst and duct of Wirsung no longer exists; entire pancreatic secretion entering duodenum *via* the duct of Santorini.

Wirsung so that finally all the external secretion of the pancreas was entering the duodenum through the duct of Santorini. (Fig. 3.)

Pancreatic Juice Findings. The pancreatic juice studied was opalescent and had a peculiar distasteful odor, somewhat resembling that of decomposing meat. The pH was 8.2. The specific gravity was 1.005. The total solid content varied from 2 to 3 per cent, of which 1 per cent consisted of organic substances.

Appetite Secretion. Although there was a continuous discharge of secretion from the tube, a great acceleration in the rate of discharge occurred after the ingestion of food. Between the time of ingestion of food and the noticeable increase in the rate of secretion there was an interval varying from 20 to 50 minutes. No relation was observed between the type of food eaten (*e. g.*, carbohydrate, protein, fat) and the duration of this interval. In order for the

acceleration of secretion to occur food had to be swallowed. Efforts to induce a "psychic secretion" were unsuccessful. The interval was interpreted as representing the amount of time elapsing before the food swallowed entered the duodenum, and there, by the action of the acid chyme on the duodenal mucosa, excited the pancreatic secretion (secretin formation).

Amount and Enzymatic Potency of the Secretion. We have set down in Table 1 the amount and the enzymatic potency of the fistula secretion collected from May 25 to June 9. During this time the patient was eating a well-balanced diet averaging 5000 to 6000 calories daily.

TABLE 1.—ENZYMATIC CONTENT OF FLUID FROM PANCREATIC FISTULA.

Date.	Drainage, cc.	Lipase units, cc.	Trypsin units, cc.	Diastase units, cc.	Total lipase secretion, units.	Total trypsin secretion, units.	Total diastase secretion, units.
May 25	1360	2.2	0.13	0.067	3000	410	9.1
26	1060	3.2	0.60	0.061	3400	640	6.5
27	1120	3.0	0.50	0.066	3350	560	7.4
28	770	3.2	0.75	0.090	2450	580	6.9
29	1390						
30	790	7.0	1.20	0.127	600	160	10.8
31	1300	1.3	0.50	0.070	1700	650	100.0
June 1	1180	2.0	1.50	0.040	2350	1780	47.5
2	890	2.3	...	...	2250		
3	920	2.15	...	...	1950		
4	130						
5	210	3.5	...	...	750		
6	620						
7	800	7.5	...	...	6000		
8	740						
9	410	5.5	...	...	2300		

As enzymes have not been isolated in pure form, their quantitative estimation cannot be based on absolute amounts by weight, but must be arbitrarily expressed by a definition which refers to their digestive potencies. Such definitions have been given by Willstätter (1923 etc.,) and his coworkers in their experimental work aiming at the purification and concentration of ferments from the pancreas and other glands. We thought it advisable to adopt their standards for the titration of the enzymatic activity of the fistula juice. This permitted ready comparison between the amount of digestive enzymes excreted through the fistula and the amount usually encountered in the gland itself.

The detailed reasons for the choice of the following "unit" definitions are to be found in the work cited above. They were chosen by Willstätter and his associates because they represent the average amount of the individual enzymes contained in 10 mg. of dried hog pancreas.

One lipase unit is the amount of lipolytic enzyme that hydrolyzes 0.6 gm. of olive oil when incubated with 2.5 gm. of olive oil at 30° C. for 1 hour in the presence of the necessary activators.

One trypsin unit is the amount of proteolytic enzyme that liberates 3 mg. of amino-N from 300 mg. of casein dissolved in 10 cc. of water at a pH of 8.9 when they are incubated for 20 minutes at 30° C. This represents about one-tenth of the amino-N of the casein susceptible of enzymatic digestion.

The definition of one amylase unit involves the calculation of the reaction constant. It amounts to approximately 100 times the amount of the enzyme that will split 25 per cent of 0.25 gm. of starch when it is incubated for 17.5 minutes at 30° C. and at pH 6.8.

For instance, 1 cc. of the pancreatic juice collected May 25 contained 2.2 lipase units, 0.13 cc. trypsin units and 0.067 amylase units. This means that within 1 hour and under optimal conditions 1 cc. would effect a 24 per cent saponification of $2.2 \times 2.5 = 5.5$ gm. of olive oil, would liberate one-tenth of the amino-N of 127 mg. of casein ($300 \times 0.13 \times \frac{60}{20}$) and in the same time would convert into sugar one-fourth of 8 gm. of starch.

It is impossible at the present time to draw a comparison of the enzymatic content between human fistula juice and human pancreas gland, since no data have been published for the latter. Deutsch and Grubel (1927) made a quantitative study of a human pancreatic cyst fluid. They found 0.0067 amylase unit per cc., which is one-tenth of the average for the present fistula fluid. Their determination of lipolytic enzyme is based on the hydrolysis of tributyrin and cannot be compared to lipase action as measured by triolein cleavage. They found that the trypsin in the cyst fluid was not in an activated state; however, they did not determine the actual trypsin content after addition of the activator enterokinase. The results of previous studies of pancreatic cyst fluids, quoted by Deutsch and Grubel, do not permit a quantitative evaluation of the enzymes.

Studies of the fistula juice from animals have been confined to dogs. Waldschmidt-Leitz and Waldschmidt-Graser (1927) compared fistula juice from dogs with the dry glands of dogs and hogs. The enzymatic content of 1 cc. of juice approximated the content of 0.05 to 0.1 gm. of dry dog pancreas for the enzymes investigated. Hog pancreas was found much richer in enzymes, especially in lipase.

If we assume that the enzymatic content of human pancreas is of the same magnitude as that of hog pancreas, then 25 gm., the average weight of a dried human pancreas, should contain about 2000 to 3000 lipase units, 2000 to 3000 trypsin units and 1000 to 1500 amylase units. The amounts discharged daily from the fistula in the present case varied from 600 to 6000 units of lipase, from 160 to 1800 units of trypsin and from 6 to 100 units of amylase.

From these observations three conclusions can be drawn: (1) There was no constancy in the ratio of lipase : trypsin : amylase on various days and no necessary relationship among the amounts of the individual enzymes secreted. Variations in the dietary constitution might have thrown some light on this question and on the question of specificity of secretin. Experiments along these lines could not be carried out, because the patient went into collapse for some reason which could not be determined when placed for a few days on an almost pure carbohydrate diet. Farrell and Ivy (1926) did not find any qualitative difference in the enzymatic content of the pancreatic excretion when dogs with pancreatic fistulas were put on extreme fat, carbohydrate or protein diets. (2) A comparison between the proportion of the various enzymes present in the fistula juice and their proportion in normal dried hog pancreas shows a relative increase in the amount of lipase in the former. This may have been due to the fact that the pancreas is practically the sole source of the body lipase. In disease of pancreas the protein- and starch-splitting enzymes may possibly be supplied by other secretions of the body (pepsin, erepsin and ptyalin, etc.). (3) There was a different rate for the secretion of the various enzymes and therefore a different rate for the discharge of the total amounts of the individual enzymes, theoretically present in the pancreas at one time, with corresponding variation in the frequency of renewal of the supply of enzymes in the gland.

There was no digestion of the tissues of the abdominal wall, despite leakage along the drainage tube. In view of the fact that such digestion does occur in some cases of pancreatic fistula, *e. g.*, that described by Fast (1930), a portion of the fistula secretion was analyzed immediately after discharge in order to throw some light, if possible, on the mechanism of digestion of the tissues of the abdominal wall.

The following experiment was performed: (1) 1 cc. of the fistula juice of May 5 was allowed to act on 300 mg. of casein for 1 hour. An increase in the acidity of the solution was not observed. (2) 1 cc. of the same secretion after activation with the amount of enterokinase obtained from $\frac{2}{3}$ gram of human duodenal mucosa for 30 minutes when allowed to act on casein for 20 minutes caused the liberation of an amount of acid neutralized by 0.3 cc. of $\frac{N}{5}$ KOH. The enterokinase was prepared from human duodenum, according to the directions of Waldschmidt-Leitz. (3) The enterokinase extract alone produced no increase in the acidity when allowed to act on casein.

In the light of these results it appears that digestion of the tissues of the abdominal wall around the wound does not occur if the trypsin in the secretion discharged is not activated. Similar experiments would be desirable in cases where tissue digestion does occur. In the case of Fast there was probably admixed a sufficient amount

of tissue juice, from the abdominal area drained, to activate the trypsin.

Summary. A case of pancreatic cyst was studied which, after operation and prolonged drainage through a fistula led to complete recovery. The course of the disease and the healing process are interpreted and the probable site of the cyst relative to the pancreatic ducts is discussed.

In a study of the enzymatic output no constancy was found in the ratio lipase : trypsin : amylase secreted. The daily output of these enzymes, when compared with their amounts estimated to be present in the gland, was found to represent a large proportion of the lipase present and a much smaller amount of the amylase and trypsin. The latter was found to be free of enterokinase. This accounts for the fact that digestion of the tissue around the wound did not occur.

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FURTHER OBSERVATIONS ON THE USE OF DEXTROSE IN PNEUMONIA.

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In a previous report[1] on the subject of dextrose therapy in pneumonia, we stated that the value of this treatment must be gauged by the results obtained in the cases that had positive blood cultures. And when we concluded, in this earlier study, that dextrose was of value as a supportative measure, we did so largely because the mortality, in our positive blood culture cases, had improved while this treatment was being used; the mortality in the positive culture

cases of our second series (1928, 1929) was 22 per cent better than it had been in the first series (1925–1928). We were impressed with this improvement, and our tendency was to attribute it to the use of dextrose.

We have continued this study, and the present report includes the observations made during the period 1929 to 1931. Postoperative collapse of lung, postoperative pneumonia and the pneumonia of children are not considered in this report.

Methods. Dextrose was given by mouth in the form of lemonade, 150 to 200 gm. to each quart, and between 1 and 2 quarts were taken each day. This dextrose drink was given routinely to all cases of pneumonia. There appeared to be a considerable variation in the ability of patients to drink lemonade, as some were able to take it freely throughout the disease, while others became nauseated in a day or two, and the further giving of dextrose by this method became impossible. In the cases that showed any degree of toxicity, dextrose was given by vein in a 25 per cent solution made up in normal salt solution. During the past year a continuous method of giving the intravenous injection was developed. As the apparatus is a simple and efficient one for intravenous therapy, a more detailed description of it will be given in another place.

The dextrose solution was given continuously over periods from 6 to 12 hours during the day, and as a rule from 1000 to 1500 cc. was received by the patient. It was continued in this way during the course of the disease. Thrombosis of the veins of the arm, unfortunately, was frequently noted after this continuous method.

An effort was made to give the greatest amount of dextrose that could be burned. In most cases, this maximum approximated between 50 and 60 gm. of dextrose per hour. Utilization of dextrose usually became unsuccessful, if the rate of intake of solution exceeded 200 cc. per hour. When dextrose appeared in the urine, it was usually because the solution had been given too rapidly. However, it is probable that, in some of the more toxic cases, the ability to burn sugar was decreased. The amounts of dextrose taken, and the timing of the inflow of solutions, were rather closely watched, and we are satisfied that dextrose was given adequately, to the great majority of the cases.

TABLE 1.—GENERAL MORTALITY AND BLOOD CULTURE DATA.

	Cases.	Mortality, per cent.	Blood cultures taken, cases.	Blood cultures, positive.	
				No. cases.	Per cent.
1925 to 1928 . .	160	43	72	19	26.3
1928 to 1929 . .	126	42	97	29	29.7
1929 to 1931 . .	249	45	218	100	47.7
	535		387		

Results.—The above table shows that the general mortality has been about the same over a period of 6 years. The number of cases in which blood cultures were taken has increased, and the actual number of cultures in the last 2 years is more than double the number of cases. We would call attention to the increasing percentage of positive blood cultures. In the last 2 years, this increase has been chiefly due to repeating the cultures on cases which were at first negative.

The following table indicates the mortality in the positive and negative blood culture cases.

TABLE 2.—POSITIVE BLOOD CULTURES.

	Cases.	Deaths.	
		No.	Per cent.
1925 to 1928	19	14	73.7
1928 to 1929	29	15	51.0
1929 to 1931	100	74	74.0

NEGATIVE BLOOD CULTURES.

	Cases.	Deaths.	
		No.	Per cent.
1925 to 1928	53	16	30.2
1928 to 1929	68	22	32.0
1929 to 1931	118	15	12.7

During the years 1928, 1929 in the positive group a considerably better mortality was noted over the previous years; but the actual number of cases was small. At this time, we were not estimating the pneumococcus count, and from what we now believe, it is very probable that our better results in this year were due to the fact that many of the positive cases represented those with very low counts per cubic centimeter of blood. The very high mortality in a much larger series during the past 2 years is in keeping with the figure generally quoted for positive blood culture cases (not serum-treated). The negative blood culture group shows a marked decrease in mortality in the last 2 years. The relatively low mortality in the negative blood culture group in the past 2 years is in striking contrast to the positive group. Practically five-sixths of the fatal cases showed positive blood cultures.

Comment. During the past 2 years we have carried out the blood culture studies on a much greater scale. This was done, first to establish more definitely the incidence of pneumococci in the blood in our fatal cases, and second to be able more easily and accurately to estimate the value of the dextrose therapy. Blood cultures were not repeated if found positive, but if negative, while the clinical course of the patient still indicated a toxic state, they were repeated a number of times. The fatal cases that had negative blood cultures during the greater duration of the disease, would nearly always have a positive culture at or near the end of the infection. Very few cases die with negative blood cultures, if the routine of repeating the cultures is closely followed. In our previous report we called attention to our very high negative blood culture mortality and stated that a more careful repetition of taking blood cultures would likely produce different results. Our present tables very clearly confirm this opinion. During the past year, blood agar plates have been made routinely at the taking of the blood culture so that the number of pneumococcus colonies could be estimated. We believe this procedure is an important one, particularly in reference

to prognosis. The plate, of course, often misses a growth that is observed in the broth. We have not encountered a case which has recovered (nonserum cases) with more than 15 colonies of pneumococci in 1 cc. of blood, and we have seen only 1 case with 15 colonies recover. In their early monograph on pneumonia, Avery, Chickering, Cole and Dochez[2] have spoken of these phases of blood culture work and it is interesting that in their group of nonserum treated cases with pneumococcus in the blood stream there were no recoveries where more than 15 colonies were found. The positive blood culture cases that recover must be those in which the colonies are very few; at least, this has been our experience. Fatal cases, however, may occur where only a few pneumococci are present. Further observations pertaining to this particular phase of blood culture work should be of considerable value and Koch[3] has informed us of an interesting study, now in press, correlating the blood culture findings and prognosis. The positive blood culture group is an important one, because the severity of the disease in any community bears a close relationship to the number that have a bacteremia. As Topley[4] remarks, the positive blood culture is an index of the severity rather than an accurate index of the presence of the organisms in the blood. Further, one is well able to agree with his statement that "the prognostic significance of a positive blood culture is one of the best attested facts which have emerged from the bacteriologic study of this disease." Any therapeutic measure that is to be considered in pneumonia must lower the mortality in this group of cases.

Dextrose has been given in adequate dosage during the past 2 years, and from the mortality figures in Table 2 there can be no other conclusion reached than that this method of therapy has failed. While we have seen symptomatic improvement frequently following the use of intravenous dextrose, and in some instances an almost dramatically favorable response, yet we are forced to admit that these good results were never seen in the positive blood culture cases where the pneumococcus count has been above 15 colonies per cubic centimeter of blood.

If we are to influence our mortality by treatment, this toxic or positive blood culture group must be affected. It is our opinion at the present time that supportative, or if we may say physiologic, methods are quite unable to accomplish this result. One wonders whether a similar series of positive blood culture cases, treated adequately in an oxygen tent, would show mortality figures any lower than those given in our tables for dextrose therapy. Osler's[5] statement made in 1888 is still true: "there is no acute disease with so few cases in which the issue of life and death lies in the administration of drugs." It appears to us at the present time, more forcefully than ever, that the only hope in treating this disease in its toxic forms, is by directly counteracting the pneumococcic infection, or, in other words, specific therapy.

Conclusion. After a fair trial in the use of dextrose in the treatment of pneumonia, we have observed that it has not reduced the mortality and have, therefore, concluded that it has no essential place in the treatment of this infection.

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A CLINICAL STUDY OF ARTIFICIAL HYPERTHERMIA INDUCED BY HIGH FREQUENCY CURRENTS.

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There are several methods of producing fever artificially in the human body. Some of these act indirectly while others act directly. The passage of high frequency currents through the body is a direct and rather quantitative procedure which can be controlled more carefully than any other method. The elevation of the temperature can be determined and accurately maintained by a simple and safe method which will be described. The use of this method in uncomplicated cases or cases not already impaired to the point of their being a poor surgical risk is practically devoid of danger. Other workers (King and Cocke[3], Neymann,[4] Hinsie and Carpenter[2]) have attempted to parallel, by this electrical method, the fever alternations of malaria therapy already used with considerable success in the treatment of paresis. We have felt that it was the

sum total of the fever bouts, rather than the short fever with intervals between, which was responsible for the clinical improvement of the paretics. This idea has its corollary in the occasional report of the subsidence of a chronic disease following an acute infection, usually respiratory, with a high temperature over a considerable period of time. Certain German workers in analyzing the results after malaria have added up the number of hours of fever above various temperature levels and have pointed out that the higher the temperature the shorter the period of fever necessary to bring about clinical improvement. Even at a temperature of 41° C. this total added up to quite a long time, somewhere around 48 hours, and at 40° C. 72 hours.

After careful survey of the clinical records of patients having high fevers, and after 2 years' preliminary work on dogs,[1] we set the limit of the therapeutic fever at 42° C. for the patient. Cases have been observed in which patients have survived higher temperatures than this, *i.e.*, insolation and sepsis. We know from our experience with 100 treatments that 42° C. is a dangerous temperature level, for more than a very short period. We can maintain temperatures slightly below this however (41.5° to 41.7° C.) for a period of at least 5 hours without difficulty or damage to the patient, and this has become our standard procedure. There are several reasons which dictate the choice of the 5-hour fever period in the treatment of disease by this method. It is the longest period well tolerated by the patient. It fits in well with the 8-hour working day for the personnel. It corresponds to preliminary studies of the thermal death time of certain cultures, especially gonococci, in water-bath experiments to be reported later, and most important of all it is long enough to be followed by clinical improvement.

At first we had great difficulty in obtaining enough power to raise the patient's temperature rapidly enough to make it possible to treat him in 1 day. The matter of heat insulation and the proper handling of the patient at all times during the procedure was another serious problem. After a great many changes the following method has now become practically standardized for the use of the "300-meter wave length" currents in this clinic.

Method. In order to eliminate the use of blankets, which are cumbersome and give the patient a sense of restraint, a cellotex chamber was built, which covers the patient and prevents loss of heat (Figs. 1 and 2). The upper portion is shaped like half an octagon. The lower half consists of a box containing a mattress, into which the upper half fits snugly, to prevent the leakage of heat. At one end a semicircle is cut to allow the patient's head to remain outside of this chamber (Fig. 2). There are 5 carbon filament lamps in the foot end of the box and 3 in the head end. These are controlled from the outside and maintain the air temperature within the box at a level sufficiently high to compensate for loss of heat by the patient through radiation, etc. (usually around 45° C.). Drapes surround the patient's neck to prevent leakage of air in this direction.

FIG. 1.—This shows the general arrangement of the cabinet and treatment machine and the various openings in the upper portion of the chamber which surrounds the body of the patient. The block-tin electrodes and the many-tailed surgical binder are visible on the top of the cabinet.

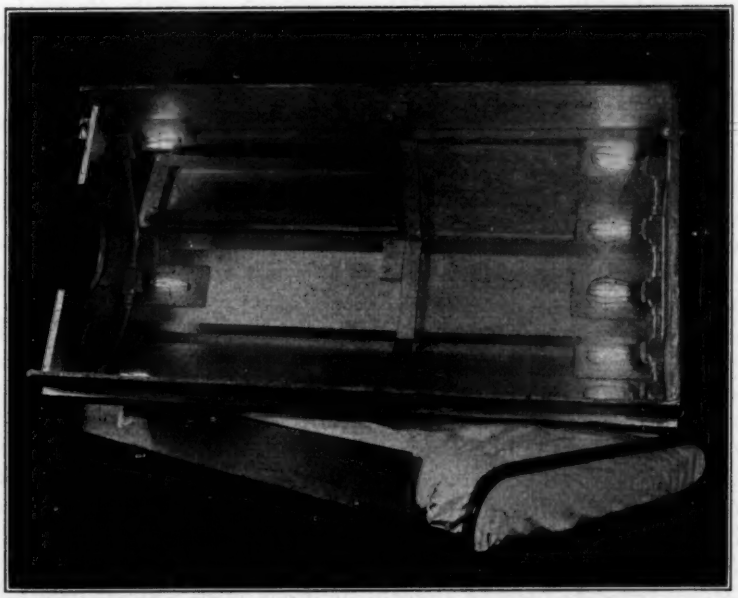

FIG. 2.—Detail of the interior of the half octagon cellotex cabinet showing the arrangement of the lights and the hole for the patient's neck.

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Various apertures for the recording rectal resistance thermometer and electrocardiograph leads, etc., are present.

The patient is placed on the mattress and block tin electrodes, 28 by 46 to 60 cm., are bound on the anterior and posterior surfaces of the trunk by means of a many-tailed surgical binder. The patient is then covered by a sheet. The electrodes are connected to the high frequency machine. The lights within the cabinet are turned on and the rectal thermometer inserted. The pulse and respiration, as well as the temperature, are recorded every 10 minutes.

The high frequency apparatus is a slightly modified "diathermy" machine able to pass 5000 to 6000 milliamperes through the patient's trunk between the block tin electrodes.

Clinical Progress. After the current has been turned on it is raised as rapidly as the patient permits to between 5000 and 6000 milliamperes. No lubricant appears necessary, since the patient begins to perspire almost immediately. During the first 10 to 30 minutes no change may occur except for the rapid outpouring of perspiration. Then there is a flushing of the skin which may progress to the point where the patient becomes a deep red color (not cyanosis). Perspiration fairly runs off the skin. Immediately after this the temperature begins to rise and continues to rise at an even rate until the current is turned off. If the elevation of temperature has been rapid the rectal temperature may continue upward about a half a degree after the current is turned off, but if the rise has been fairly slow this continued rise will be reduced or may not occur. This is apparently due to the redistribution of the heat which has been absorbed by the trunk in the neighborhood of the electrodes. During the elevation of the temperature the rectal temperature is at first higher than the mouth temperature. When the body temperature reaches about 38° to 39° C. the mouth temperature usually becomes higher than the rectal temperature and remains so or equals it until the current is turned off. This, we believe, is due to the heating up of the lung substance faster than the blood can remove the stored heat, so that the expired air is hotter than the blood in the rectal vessels. As soon as the current is turned off the mouth temperature equals or becomes slightly less than the rectal temperature (Fig. 3).

When the required temperature level has been reached and the current turned off, the electrodes are removed from the trunk and the patient remains in the box covered only by a sheet. The air surrounding the patient is kept at an adequate level, and in so doing the patient's body temperature is maintained at the predetermined height. If, for any reason, the body temperature rises the surrounding air is cooled off. If it drops the air temperature may be raised as high as it can be tolerated (perhaps 50° C.) and slowly the body temperature is built up to the desired level.

Many patients become slightly delirious even though mentally normal beforehand. They are hypersusceptible to slight noises

and are apt to become excited and pugnacious. They sometimes lose all mental restraints and barriers, and their speech reverts to their fundamental type. With this excitement the pulse and respiration mount rapidly. If they are not quieted heat is produced by physical exertion in sufficient quantity to raise the body temperature still further (Fig. 4). Immediate measures must be taken to quite the patient for the temperature is already near the upper safe limit. Often calmness and reassurance on the part of the

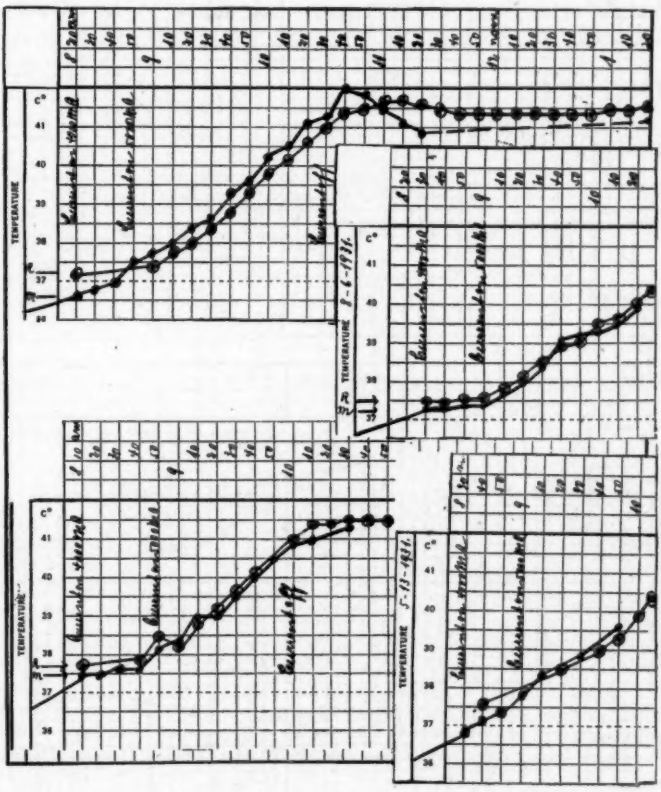

FIG. 3.—This chart shows the vagaries of the mouth (dots) and rectal (circles) temperatures during the establishment of the fever.

attending doctor and nurse, stroking of the patient's head, requesting him to be quiet while the blood pressure is taken and similar maneuvers are sufficient to quiet the patient. Many sedatives have been tried, but none well suited for general use has been found. All have some more or less serious disadvantage, the chief of which is the period of excitement produced by the drug before the narcotic stage is reached. Nearly all are depressants of the respiration or blood pressure or both. This is in keeping with

clinical experience with patients in delirium during high fever. Chloral hydrate in doses up to the narcosis point has been very

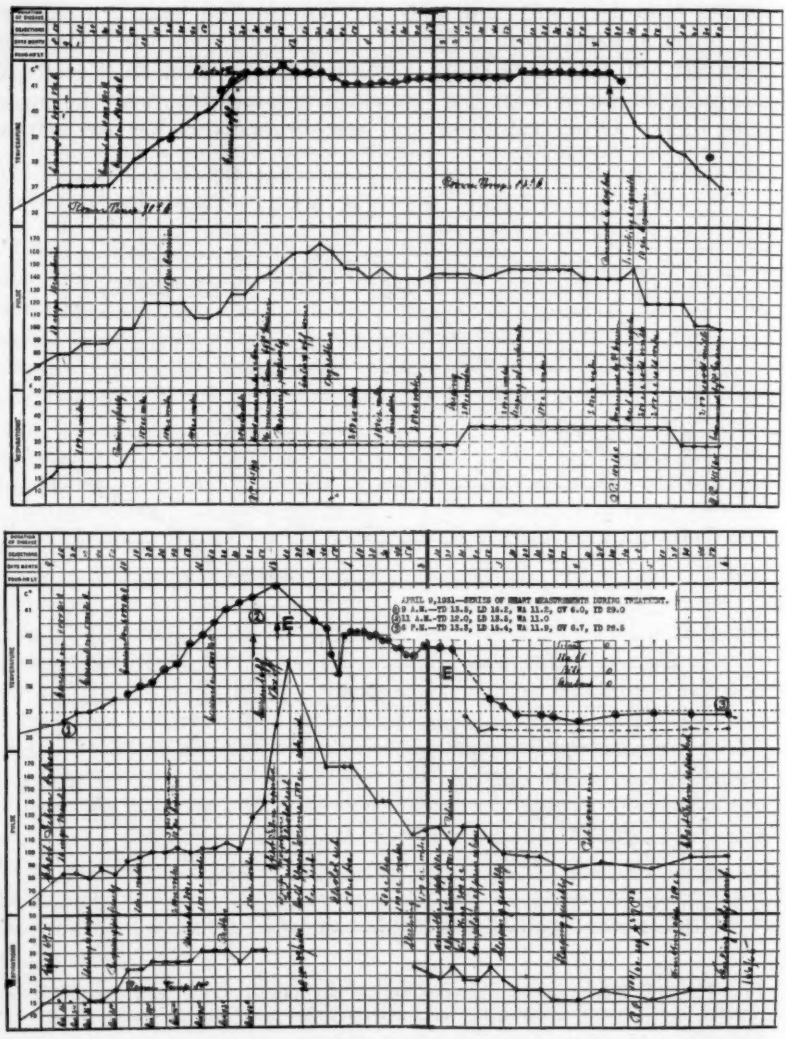

FIG. 4.—This patient had one treatment with the usual sequence of events (upper chart). A month later, during his second treatment, the patient became excited before enough sedative could be given and started doing his "setting up exercises." The exertion caused his temperature to rise to 41.9° C. and the pulse to 250 per minute and the respiration to a very high irregular rate. Ice rubs and air cooling and cold enemas (*E*) brought the temperature, pulse, and respiration down to their normal level.

effective, though at times even this amount is not ample. An occasional patient requires no sedative.

The pulse and respiration usually rise in keeping with the temperature (Fig. 3, *ff*). The pulse usually reaches a level between 130 and 150, where it may be maintained for the duration of the treatment. Periods of excitement are always indicated on the chart by a rise in the pulse rate. In nervous patients the entrance of the doctor or visitor can almost be registered by changes in the pulse of from 10 to 20 beats. During excitement the respiration may vary greatly as will be evident in some of the charts shown (Figs. 4 and 5). During the treatment the patient is allowed to drink as much warm fluid as he requests and is also given food if he wishes it.

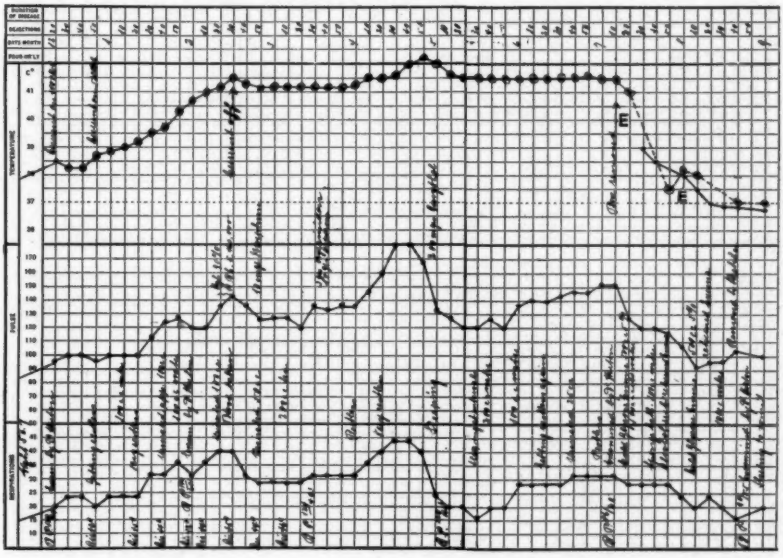

FIG. 5.—This chart shows the simultaneous variation in temperature, pulse and respiration as a result of restlessness. The effect of sedatives, cooling measures, and the subsequent continuation of the treatment as the patient quieted down are well illustrated.

When it is desired to terminate the fever the box is removed from over the patient and the body exposed to room air. It is possible to allow currents of very cool air to blow across the patient without causing a subsequent ill-effect. A drop in temperature of about 4° C. of the skin surface is apt to cause local shivering and contraction of the hair follicle muscles. If this occurs the patient is uncomfortable, and it is better to cover the body with a sheet. If nothing further is done the body temperature will gradually return to normal in about 3 hours. This may be expedited somewhat by alcohol and ice rubs, but these are not very efficient since the skin capillaries contract at the touch of the cold, and heat is

retained rather than radiated. It was found that a cold retention enema would greatly hasten the cooling process (Fig. 6). After

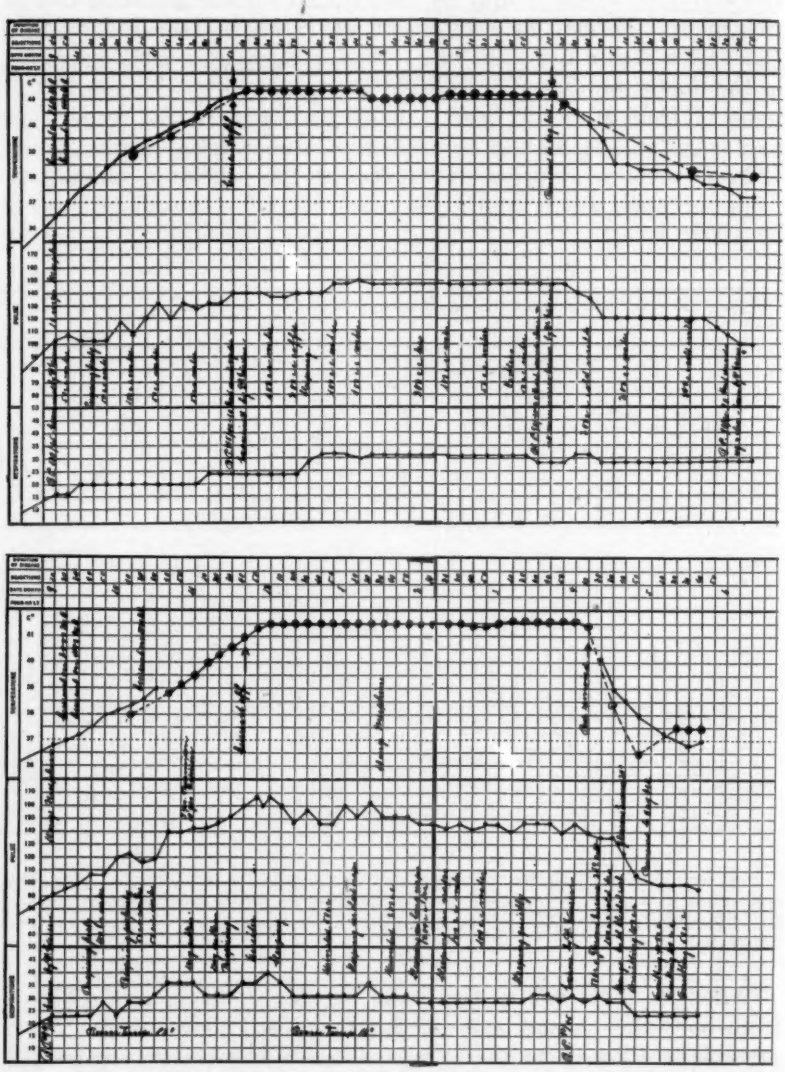

FIG. 6.—Temperature, pulse and respiration curves in a 50-year-old patient with chronic arthritis. Circles represent the rectal, and dots the mouth temperature. The lower chart illustrates a second treatment one month later and shows the effect of a cooling enema as compared to the upper curve where none was given. At this stage of development of the technique, treatments were restricted to 4 hours in cases of arthritis. Pulse and respiration curves show the normal variations.

removing the box 500 cc. of 0.6 per cent saline containing 25 gm. of glucose are instilled per rectum. The temperature of this fluid

may be as low as 10° to 15° C. without causing shock. Abdominal cramps are practically always present, but they are not severe. After 20 minutes or more another 500 cc. are given per rectum. By this procedure the temperature returns to normal within 1½ hours after the removal of the box.

The patient should never leave the treatment room until the temperature has returned to normal. It is necessary to record the temperature only at hourly intervals thereafter for 4 hours. We have found in a few cases sent back with temperatures higher than normal that the temperature rose subsequently, but removing the covers was sufficient to bring it down again. In no patient who was returned with a normal temperature has there been a rise at a later period. We have not found the mouth temperature to go below 36.5° C.

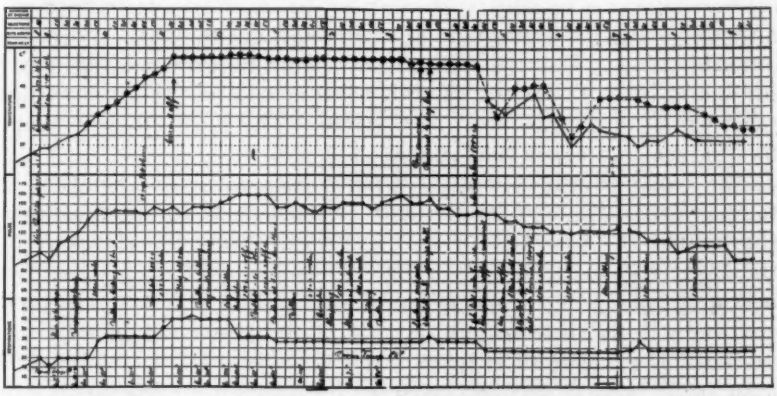

FIG. 7.—This was an obese 57-year-old arthritic patient who responded in the usual way to the fever treatment except for the delay in the fall of the temperature upon exposure to room air. Two cold enemas lowered the level of the temperature, but two hours longer than usual were required to bring the temperature back to its normal level. Further enemas were contraindicated because of vomiting and dropping blood pressure. Note the influence of the cold enema on the mouth temperature.

Immediately after removing the patient from the box the pulse and respiration begin to return to their normal, though occasionally both may remain slightly above their original levels for some time. The patients are given cold fluid to drink after removal from the box, though this is restricted to about 1000 cc., especially if a large amount was taken in during the treatment period. Too large an intake is apt to result in vomiting when the patient moves about or when he is shifted back to his own bed. Cold ginger ale, probably because of its sugar and alkaline content, is very well tolerated during this last period. Too much fluid intake may produce acute syncope in the period just after the enema is given, and in 1 patient who developed this symptom it was possible to demonstrate that the fluid content of the blood was greatly increased.

It occasionally happens in obese people that the temperature does not come down as rapidly as it should (Fig. 7), possibly due to insulation by the layers of fat. Colder enemas should thus be given to obese people than thin ones and a longer period expected for the return of the temperature to normal.

The color of the patient is a good index of his condition. This, together with the blood pressure and the temperature record, are three most valuable aids in indicating the patient's condition. Cyanosis of the lips, a beginning pallor especially of the face about the mouth, even if not accompanied by other changes, is a warning sign of failing peripheral circulation. It is usually followed very soon by a drop in systolic and diastolic pressure. The respiration may or may not change. If the respiration decreases in rate at such a time the temperature may rise, probably because of the reduced loss of heat by means of the expired air. A change in color (pallor) is usually accompanied by a stage of excitement, although sometimes the stage of excitement occurs first. With the onset of these symptoms, the patient should be watched very carefully, and if they continue the box is removed and the temperature returned to normal as soon as possible. The most efficient agent for this purpose is the cold enema.

The blood pressure (Fig. 8) usually rises with the elevation in temperature, although occasionally it remains at its original level throughout the treatment. If it has risen during the elevation of the fever it usually begins to fall when the patient reaches the maximum of his flush and perspiration (39° to 40° C.). It then continues to fall throughout the rest of the treatment period, and in the average patient reaches a rather constant level in the last hour of 80 mm. of mercury systolic, 60 diastolic. Occasionally in patients who already have a systolic pressure of around 100 there may be a steady fall from the beginning of the treatment. It usually reaches in such a case the low level of 70 systolic, 60 diastolic. The lowest pressure which we have seen was reached in a patient who had been chronically invalided by arthritis for a long time. She reached the astoundingly low level of 40 systolic and 30 diastolic, which she maintained for a considerable period (3 hours) without any other evidence of difficulty, and with a gradual return to a 90 systolic and 70 diastolic the next day.

In general, electrocardiograms show the decrease in voltage of the action currents of the heart consistent with a low blood pressure. While there are other changes apparent in the electrocardiograms, their exact relation is not clear.

The general reaction of the patient throughout the treatment can be improved by close attention to a great many small details. The room should be darkened. All noise should be eliminated as much as possible. A registering or indicating thermometer makes it unnecessary to disturb the patient to take the 10-minute rectal

temperatures, thus allowing him to sleep as much as possible. An atmosphere of calmness must be created by the personnel. Sedatives should be given to make the patient doze but not enough to

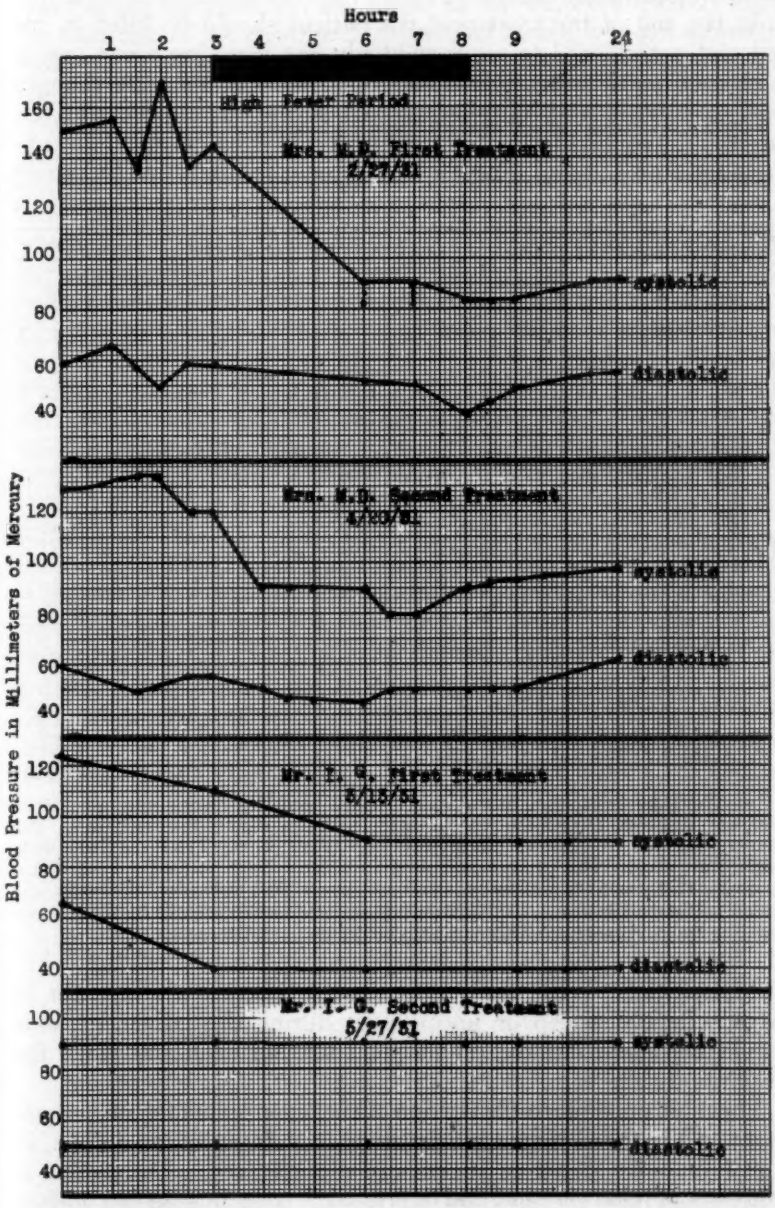

FIG. 8.—These 4 typical curves of the variations in the blood pressure cover the usual ranges. The pressure is generally lower and shows less fluctuation during the second treatment.

make it difficult to ask him questions about his sensations and to get him to drink the amount of fluid necessary to maintain the proper water balance. Two to 4 kilos of weight may be lost during the treatment from waterloss.

At the end of the treatment the patient should be lifted to his bed and not allowed to move suddenly lest vomiting occur, which may continue if once started for some hours. We have thought that paraldehyd and morphin, as well as the barbital derivatives, intensified the vomiting after treatment and even caused it to continue for 2 or 3 days. This happened too consistently to be purely

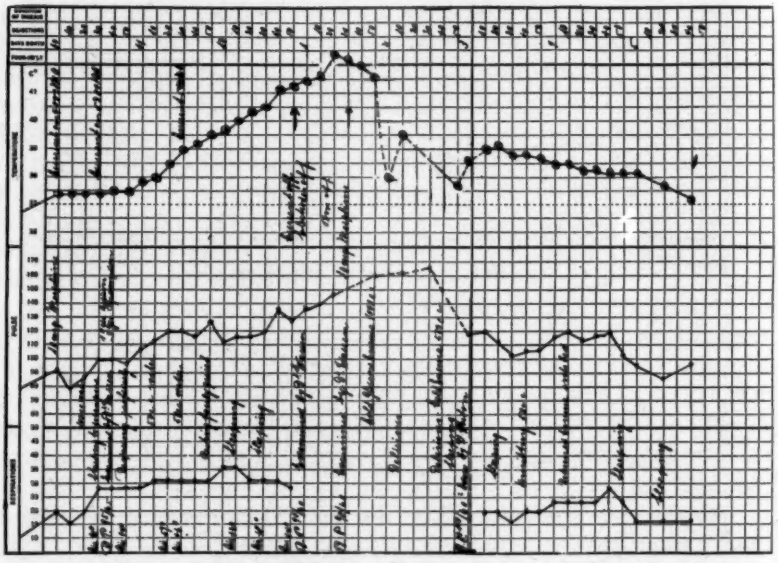

FIG. 9.—This paretic patient suddenly stopped breathing during treatment while sleeping. Artificial respiration was necessary six times during the next hour. The temperature rose to 42.4° C. The pulse and blood pressure changed very little during this period. This patient swallowed his tongue whenever his head rolled face upward. This was finally discovered and the tongue held out with a hemostat and caused no further trouble. The temperature was reduced efficiently by cooling and instilling two cold enemas. This patient is on parole (3 treatments).

circumstantial. With badly degenerated paretics who are apt to become deeply asleep or unconscious during the treatment, care should be taken that the tongue does not fall back and block the respiration (Fig. 9).

The most uncomfortable portion of the fever period for the patient occurs while the patient's temperature is at from 39° to 40° C., at which time the sedatives are usually administered. The patient is restless and feels very hot and oppressed. A slight delirium is often noted. It is a great relief to the patient when the temperature rises above 40° C., as these sensations then disappear to a great extent.

The patient relaxes and usually sleeps in short naps without further sedatives. The patient, of course, feels quite hot throughout the treatment. He is apt to feel very tired near the end of the 5-hour elevation in temperature, and unless he has been told exactly about the duration of the treatment beforehand he is apt to get somewhat restless. This can often be prevented by placing a clock where he can see it during the last hour of the treatment. It is not wise to push the sedative too much at this time, since the patients are apt to sleep soundly as soon as the temperature drops, and it would be impossible to force fluids after the treatment is over. The latter is an essential portion of the recovery period because the patient is apt to feel weak the next day if his fluid intake has not been sufficient.

The ambulatory patient in good general condition is allowed to go home by noon the day following treatment unless he comes from a considerable distance, in which case he is kept over another day. Except for nausea which could be attributed directly to the narcosis and occasionally weakness lasting for a few days, there have been no deleterious after effects. This, of course, does not include the occasional burn under the electrode. These have responded well to tannic acid dressing and usually heal in about 10 days without difficulty. They are rarely more than simple blisters. One in our series was followed by a keloid which had to be treated with radium.

Results. One hundred treatments have been given to 57 patients, from February, 1930, to August 1, 1931. The artificial hyperthermia procedure has been greatly modified and refined within this period. The method now used will give good results in careful hands with properly selected patients. We feel that the conditions under which we had to work and the type of patient whom we treated at first were not of the best. There have been 2 fatalities.

TABLE 1.—TYPES OF CASES TREATED BETWEEN FEBRUARY, 1930, AND AUGUST, 1931.

	Cases.	Treatments.
Syphilis, C. N. S. (paresis)	18	33
Arthritis, chronic (infectious and noninfectious)	15	26
Arthritis, G. C.	9	16
Vaginitis, G. C.	2	4
Meningitis, G. C.	1	3
Multiple sclerosis	3	4
Encephalitis, chronic	1	3
acute	1	1
Hypernephroma	1	3
Miscellaneous	6	7
Total	57	100

Oldest patient, aged 65 years; youngest patient, aged 3 weeks.

Case Abstracts. CASE 1.—The first fatality occurred with the second patient treated: a colored girl, aged 25 years, who had just recovered from alcoholic hallucinations. She had central nervous system syphilis and her mental status was poor. Her prescribed antisyphilitic treatment was not

consistently pursued because of her drunkenness. She rarely took treatment at the proper interval. After recovering from the delusional state she seemed to be in good general condition on physical examination. In view of this fact and the difficulty in giving her the regular form of treatment, artificial fever therapy was suggested and attempted. At that time blankets were used to prevent the patient from losing heat. These caused a sense of restraint and the patient was apprehensive about this. After a good deal of trouble with the treatment machine the temperature was finally elevated at the end of six hours to 41.5° C. by mouth thermometer and 42° C. by rectal thermocouple. This was maintained for about 1 hour, when the patient became delirious and struggled violently to get out of bed. She became short of breath. The covers were removed. She vomited a large amount of fluid, and the pulse and respiration stopped. The patient could not be resuscitated. The pulse rate at its highest was 170 per minute and the respiration 45. At autopsy there were small hemorrhages in the epicardium such as are seen after sudden death, a somewhat enlarged thymus, and no obvious cause to account for the sudden exitus. The final diagnosis was chronic alcoholism, central nervous system syphilis, hypertrophy of the thymus. After much discussion it was concluded that chronic alcoholism was the major factor in the demise of this patient.

Case 2.—The second fatality occurred almost exactly 1 year later. This patient was a white woman, aged 26 years, with a diagnosis of chronic encephalitis lethargica, with symptoms of 8 years' duration. She had been steadily going down hill in spite of various therapeutic measures. Among other symptoms, the patient was subject to attacks of noisiness, screaming and crying, with seizures of twitching of the extremities, vertical nystagmus and incontinence, lasting 24 to 48 hours. These attacks were repeated at intervals of from 2 to 3 days, and had increased in severity and number during the last 6 months of her life. The patient was given an artificial fever treatment on February 27 and another on April 20, 1931, with marked improvement in the symptoms. A third treatment was started on May 20. The temperature rose in the same manner as it had on the previous occasions, and the current was shut off at the end of 2 hours, when the temperature had reached 41° C. The temperature then rose to 41.5° C. in the usual manner. Suddenly the patient began to have one of her usual attacks except that it was of marked severity. The blood pressure began to drop, and within about 1 hour had fallen from 100 systolic and 60 diastolic until it could no longer be measured. The radial pulse was not palpable. The heart rate continued unchanged. The sounds were of good quality. The color, of course, changed to a pallor. The respiration became slower and slower and finally irregular. The head was lowered and various medications tried without effect. The temperature began to rise steadily as the respiratory rate decreased, and when the respiration had almost completely ceased the temperature reached 43° C. The patient was put in an ice pack and given an ice cold enema which was not retained. Various mixtures of oxygen and carbon dioxid were successful in stimulating the respiration for about 1½ hours after this. There was very little cyanosis as long as the respiration and heart rate were maintained. When the respiration began to fail, in spite of the oxygen and carbon dioxid mixture, the patient was put in a Drinker respirator. The heart was failing, and it stopped entirely by the time that the neck piece of the respirator was adjusted. The temperature had fallen to 40° C. before the heart stopped.

Autopsy showed no variation from the normal in any of the organs except for the few epicardial hemorrhages such as are commonly seen in acute exitus. The heart was otherwise in good condition; the muscle well developed. It was not dilated. The brain showed no gross or microscopic lesions on careful search. The results of studies with special stains are not

yet available for report. Chemical analyses made on the heart's blood 1 hour after exitus showed: Nonprotein nitrogen, 43 mg. per 100 cc.; chlorid, 460 mg.; sugar, 95 mg. per 100 cc.; hematocrit, red blood cell content, 51 per cent. In other words, there is no evidence from the data at hand to explain the cause of death.

This case illustrates the rise in temperature coincident with the drop in the respiration rate. The failure of the circulation to maintain the blood pressure was probably due to the peripheral dilatation which did not respond to the usual stimuli. The ice packs failed to be of use either in bringing down the temperature or in raising the blood pressure by contracting the peripheral vessels of the skin. A continuous cold enema seems to have been the most effective agent in bringing the temperature down from the high point to 40°. The period above 41.5° was approximately 15 minutes in duration, which of itself should not have been the cause of death. The fall in pressure and the failure of the respiration were apparently the main contributing factors.

It is felt that the first fatality could have been avoided if the treatment had been conducted with the present technique. The possibility of damage to the respiratory mechanism in patients having central nervous system lesions increases the risk of treatment in such cases. All those concerned realized before treatment that the patient with the chronic encephalitis was a very bad risk. The treatment of similar cases should be undertaken with caution.

In summarizing our experience with 100 treatments of 57 patients having various diseases, we feel that the contraindications for treatment are somewhat similar to those which would hold for an abdominal surgical operation. Chronic alcoholism and obesity, arteriosclerosis with its possibility of a ruptured vessel in case the pressure should rise too high during the first stages of the fever, central nervous system lesions involving the respiratory mechanism, cardiac damage with lowered cardiac reserve are all specific contraindications. The blood pressure readings still remain the simplest index of the efficiency of the vascular system during treatment.

Preliminary Clinical Results. The first patients treated were chosen from a group of badly disoriented and degenerated paretics. Some of these were in very bad physical condition. Two who were especially disintegrated, and who had been in bad physical condition for many months, were given artificial fever and tryparsamid, but they continued to go down hill and died several months after the fever treatment. The rest have shown great clinical (Fig. 10) and psychic improvement and gains in weight of from 20 to 30 pounds. All have been paroled, and of the 14 only 1 has relapsed, but this patient has had only 1 treatment of a 5-hour fever. The remainder have had from 2 to 4 treatments at intervals of from 10 days to several months apart. The chemical changes have been consistent and resemble the changes after malarial therapy. The

gold sol. curves, the protein and the number of cells in the spinal fluid returned to the normal. The Wassermann reactions in the spinal fluid and blood have changed somewhat but have not yet become negative. The shortest period between treatment and parole was 5 months, the longest 9 months.

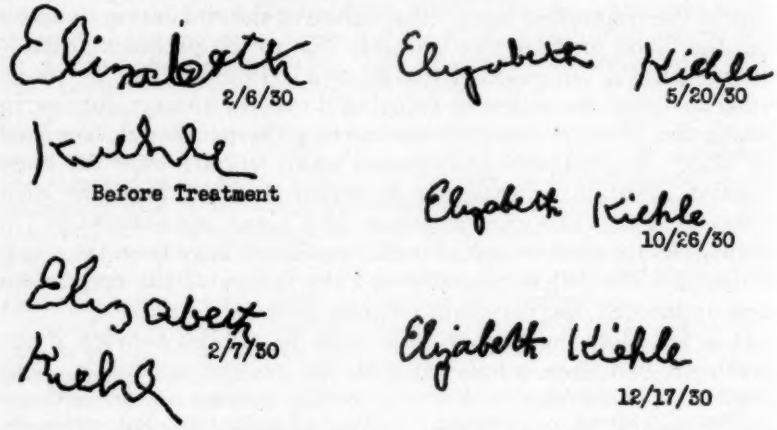

FIG. 10.—This group of signatures illustrates the subsidence of the ataxia in a paretic patient after four artificial fever treatments. The patient is on parole.

The next series treated was an arthritic group. In this group those who responded most were patients suffering with arthritis of gonorrheal origin. The acute lesions subsided rapidly, lost their redness and tenderness, and there was gradual recovery from the stiffness. The chronic lesions became painless and there was gradual relief from the stiffness, with increased mobility. Two treatments were given from 10 days to a month apart. The effectiveness of the 5-hour fever period in gonorrheal infection is supported by water-bath experiments on the thermal death time of gonorrheal cultures, the results of which will be reported elsewhere. A series of patients with chronic infectious arthritis with soft tissue proliferation and bone atrophy or with joint destruction was treated next. Immediate relief from pain occurred and in some patients joint pain has not returned within a period of 8 months. There has been increased mobility (Figs. 11 and 12) and a reduction in the size of the soft tissue swelling. As the patients have used their joints more, some of them have been troubled with muscle pains. The usual rehabilitory measures are, of course, necessary after the fever treatment. It is too early to speak of the permanent results in arthritis at this time. This will be reported elsewhere at a later date.

Gonorrheal vaginitis and cervicitis in adults has been cleared up in from 1 to 2 treatments with no evidence of infection by

culture or smear after the next menstrual period following treatment. These cases had all been resistant to the usual forms of therapy.

FIG. 11.—The appearance of the hands of a 50-year-old patient with advanced arthritis. This shows the maximum extension before treatment.

FIG. 12.—The hands of the same patient 1 month after fever treatment showing the increased mobility of the joints. This has been retained for 7 months.

Other disease entities have also been treated, but the number has been too few and the time too short to draw any conclusions from these cases. We wish to emphasize that the above statements are tentative and are based upon periods of observation of relatively short duration, the longest that the patients have been under observation being only 1½ years. It can be stated definitely that immediate clinical improvement in the paretic group, certain types of the arthritic group and the group having gonorrheal infections is very encouraging. How lasting these results will be can only be determined by observations over a longer period of time.

Summary. Artificial hyperthermia can be carefully and accurately controlled by a rather standardized procedure well within the scope of the average hospital. The whole body temperature is elevated by the passage of high frequency currents through the trunk by means of large block-tin electrodes. The temperature is maintained at any desired level below 42° C. for 5 hours without danger to a patient in ordinary physical condition. This is accomplished by keeping the patient surrounded by air at a temperature sufficiently high to compensate for losses by radiation, etc. The temperature can be lowered at will by cooling the patient's environment, by cold drinks and, most important, by a cold enema. The condition of the patient is determined by temperature, pulse and respiration readings taken every 10 minutes, by blood pressure determinations at frequent intervals, and by noting the color of the skin. The fluid balance should be maintained. Excitement is avoided by proper sedatives and calmness on the part of the personnel.

One hundred treatments have been given to 57 patients in 19 months, with a mortality of 2 per cent, based on 100 treatments; if based on the number of patients then the mortality is 3.5 per cent.

A careful selection of patients should be made until sufficient experience with the method of treatment by artificial hyperthermia has been acquired to evaluate the possibility of damage to patients in poor condition.

NOTE.—We wish to express our great appreciation for the coöperation of the various members of the clinical services who have referred these cases to us for treatment. Especial thanks are due to Dr. William S. McCann, Chief of the Medical Service; Dr. J. R. Murlin, Director of the Department of Vital Economics; Dr. Eric Clarke, in charge of the Division of Psychiatry; Dr. F. D. Streeter, Clinical Director of the New York State Hospital; Dr. R. Plato Schwartz, in charge of Orthopedics, and Dr. Charles Carpenter for their suggestions and criticisms of the method of treatment; Dr. G. H. Whipple and Dr. W. B. Hawkins for their very careful postmortem study of the 2 fatal cases; Dr. W. R. Whitney, Director of Research of the General Electric Company for a great deal of technical advice and interest in the methods used; Mr. A. Page, of the General Electric Company, and Mr. H. E. Gordon, of the Rochester Telephone Corporation, for many helpful suggestions; Mr. Charles Renaud, of the General Electric X-Ray Corporation, for the loan of certain equipment. This work has been supported by a special grant from the Rockefeller Foundation.

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BACILLUS PROTEUS SEPTICEMIA WITH RECOVERY.

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Although Bacillus proteus is often associated with a multitude of inflammatory conditions in man, its occurrence in septicemias and bacteremias is extremely rare. As early as 1902 Berthelmann and Mau[1] reported its presence in the blood stream of a case of urethral fever and pyelonephritis. Since this publication, case reports have appeared from the hands of Jochmann,[2] Lenhartz,[3] Goebel,[4] Maymone,[5] Reye,[6] Warren and Lamb,[7] and Irimonoiu and Popa.[8] In the case of Warren and Lamb, the antemortem blood culture showed an unidentified Gram negative bacillus while the postmortem cultures yielded an organism of the B. proteus group. Irimonoiu and Popa's organism was also obtained at autopsy. Most authors agree that the organism is rarely recovered during life. In view of the rarity of the infection, we desire to present an unusual case of B. proteus septicemia with recovery.

Case Report. Patient R. D. F., aged 24 years, primipara, was referred to us through the courtesy of Dr. J. T. Smith, Jr., July 15, 1931. She was admitted to Maternity Hospital July 9, 1931, for the purpose of inducing labor, since the child was too large for the contracted pelvis. A Voorhees' bag was inserted July 10, 1931, at 11.45 P.M. and was expelled 8 hours later. Labor began about 3 hours after induction, and was completed by podalic version after manual dilatation July 11, 1931, at 11.45 P.M.

The pregnancy was uneventful and at no time were there any symptoms suggestive of genitourinary disease. A short time prior to delivery the patient began having an irregular temperature ranging from 38° to 39° C. (see temperature chart). This continued until the fourth postpartum day, when she had three very severe chills, which were followed by a temperature of 40° C. An irregular, septic type of temperature, accompanied by

frequent chills and drenching sweats continued for 60 days. The chills were of unusual severity, lasting from 30 to 60 minutes. Apart from a feeling of exhaustion the patient was apparently comfortable during the remissions in fever.

Physical Examination. A well-developed, well-nourished young female apparently comfortable. Her skin was moist, and without pallor. Pupils were equal and reacted normally to light and accommodation. Teeth were well preserved. The tongue was moist and slightly coated. Lungs revealed no abnormalities. The cardiac dullness was normal, and normal sounds unaccompanied by murmurs were elicited by auscultation. Abdomen was slightly distended, not tender. Uterus was palpable in lower abdomen, not tender and apparently involuting satisfactorily. Liver and spleen were not palpable. No tenderness in the region of the kidneys. Reflexes were normal. Lochia were normal.

Laboratory Tests. Urinalysis revealed albumin (1 +), with numerous pus cells and bacteria. White blood cells, 6400. Urine culture was positive for B. coli. Blood culture was negative after 72 hours. Routine treatment for pyelitis was instituted but no definite improvement took place.

Course. July 17, 1931, the abdominal distention increased and was accompanied by tenderness in the right flank and lower right quadrant. No mass was palpable. Three days later the distention lessened, and a hard, irregular, slightly tender mass was palpable to the right of the uterus. Vaginal examination revealed a firm, nonfluctuating, irregular ovoid mass quite high off the right cornu, which was sensitive at a point over the scar of a former appendectomy. The fundus was in the midline, and showed normal involution. The mass gradually disappeared in 2 weeks. Urine continued to show varying amounts of albumin with numerous pus cells and bacteria. A residual urine averaging 150 cc. was noted at this time.

Cystoscopic examination revealed a severe degree of cystitis. Both ureters were slightly edematous and were catheterized without difficulty. A steady flow was obtained from the right side, and an intermittent flow from the left. Bladder urine showed numerous pus cells. Right kidney urine showed 8 to 10 white blood cells, the left 4 to 6 white blood cells per high-power field. Cultures revealed B. coli. A retention catheter was inserted. At this time the blood leukocyte count ranged from 15,000 to 27,000, with a gradually developing secondary anemia. Red blood cell 3,890,000. Hemoglobin 62 per cent (Sahli).

August 4, patient was transfused with 250 cc. of whole blood. This was followed by a slight improvement in the red count, without any change in the clinical course. Fever and chills continued, and the patient began showing more marked exhaustion, with anorexia and mental depression. Transfusion of 500 cc. of whole blood was repeated August 12 and August 16. Repeated urine cultures revealed the presence of B. coli. Blood cultures at this time were negative.

August 15, there was swelling and tenderness of the left ankle, which gradually spread to the calf and thigh, with an apparent increase in the general reaction. September 3, 1931, left thigh was slightly edematous, and no tenderness was present. Abdomen was soft, not tender, spleen and liver not palpable. Vaginal examination revealed a normal uterus, without any inflammatory masses in the adnexa. Urine showed a negative albumin with fewer pus cells and bacteria. Red blood cells, 4,690,000. White blood cells, 16,700. Hemoglobin, 70 per cent (Sahli). Differential: Polymorphonuclears, 84.5 per cent; large lymphocytes, 1 per cent; small lymphocytes, 6.5 per cent; transitional cells, 7.5 per cent; basophilic cells 0.5 per cent.

September 5, little change was noted in the patient's condition. A new blood culture revealed the presence of B. proteus. The patient's blood

agglutinated the organism in a dilution of 1 to 640. At this time a definite change in the clinical course was noted. The chills became less frequent, remissions in temperature lasted 24 to 36 hours, and there was a gradual decline by lysis.

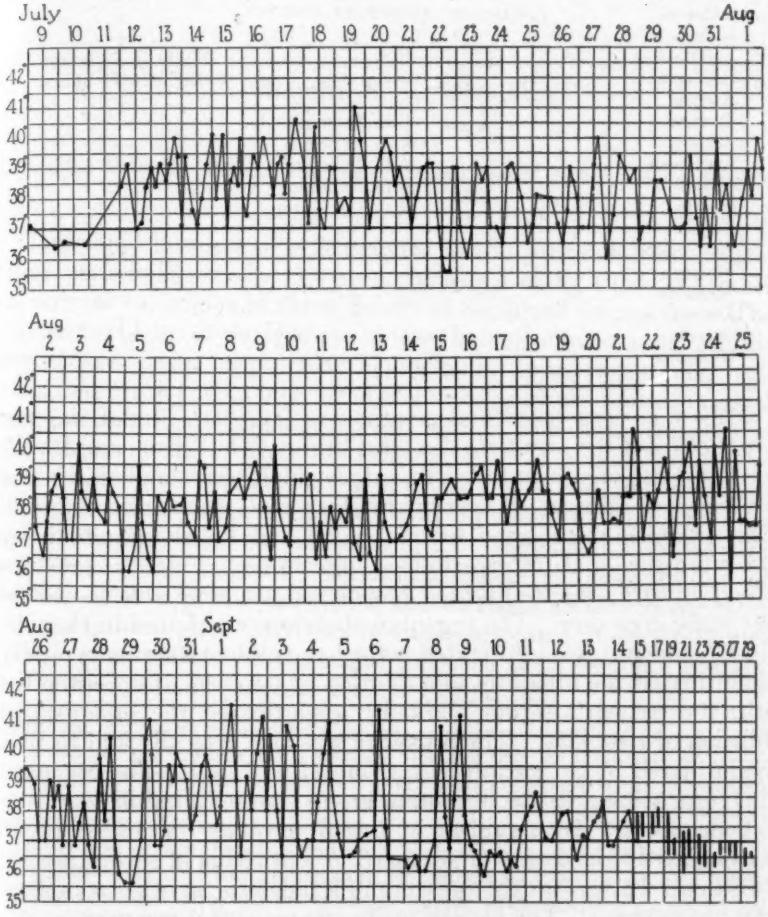

FIG. 1.—Temperature chart from admission to discharge. Noon of each day is indicated by the vertical line midway between the date figures. For the last 16 days, only maximum and minimum figures are given. Here each vertical space represents 2 days. Pulse was proportional to temperature.

The urine was clear and albumin free, with very few pus cells and bacteria. Red blood cells, 4,710,000; white blood cells, 8800. Hemoglobin, 70 per cent (Sahli). The patient was discharged from the hospital September 19, to continue her convalescence at home. Apart from the three blood transfusions and supportive medication no other therapeutic measures were instituted.

Bacteriologic Findings. The blood was drawn at the beginning of a chill, and cultured on brain broth. Incubation at 37° C. for

24 hours yielded a pleomorphic Gram negative and motile rod which gave a smooth, spreading growth (H form) on blood agar plates. The sugar reactions were as follows:

Sugars	Acid	Gas
Glucose	+	+
Galactose	+	+
Levulose	+	Slight in 72 hours.
Glycerol	+	Slight in 72 hours.
Xylose	+	+
Dextrin	± in 72 hours	−
Adonitol	± in 72 hours	−
Arabinose	± in 72 hours	−
Inulin	± in 72 hours	−
Salicin	± in 120 hours	−
Lactose	−	−
Saccharose	−	−
Maltose	−	−
Mannite	−	−
Dulcitol	−	−
Starch	−	−
Raffinose	−	−

Milk was peptonized and gelatin was liquefied. Indol was not produced and the organism bleached litmus. On Wilson and Blair's medium, the organism failed to reduce sulphite to sulphides in the presence of glucose. Acetylmethylcarbinol was not produced. The organism hemolyzed human blood and killed mice both by subcutaneous and intraperitoneal injections. From a previous blood culture, which appeared hemolyzed, we were able to isolate the same organism. The organism therefore was found in two distinct blood cultures. As stated before, the patient's serum typically agglutinated the organism in a dilution of 1 to 640. On September 5th, the patient's serum markedly agglutinated the organism in dilution of 1 to 1280. The organism was also typically and to titer agglutinated by an antiproteus serum (1 to 1280). The organism therefore belongs to the B. proteus group (species mirabilis).

Conclusions. An organism of the B. proteus (mirabilis) group was isolated from a case of postpartum septicemia of several weeks' duration. Except for the presence of a phlebitis no other complications were noted. The patient made an uneventful recovery.

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THE EFFECT OF EXERCISE ON HUMAN ERYTHROCYTES.

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The rapid increase of erythrocytes in the peripheral blood after short periods of exercise has been confirmed many times in studies on normal variations in the numbers of red-blood corpuscles.[1] The related problems of the changes in total hemoglobin content, volume percentage, mean corpuscular hemoglobin, mean corpuscular volume, and mean corpuscular hemoglobin concentration after marked exertion have been investigated less often. The data presented in this paper indicated that immediately after 2-minute periods of hard exercise, the total numbers of erythrocytes rose to a peak and fell to their normal average in about 45 minutes. This marked rise in numbers was not accompanied by significant variations in total hemoglobin content, volume percentage or concentration of the hemoglobin in the cells, with the methods employed for their determinations. Real decreases in values appeared, however, immediately after exercise in the mean corpuscular hemoglobin content and in the mean corpuscular volume (Table 1).

Method. The 40 experiments reported here were grouped into 3 series of 10 studies each, made on 3 persons respectively, and 1 series of 10 on 10 different individuals. All subjects were healthy young women between the ages of 20 and 35 years. Only 2 of the 13 persons under observation were accustomed to severe exertion.

The course of the investigation was the same in each of the 40 studies. A 2-minute period of hard exercise in the nature of running up and down 3 flights of stairs twice (21 steps each; height, 7½ inches; flights set at an angle of 31.7 degrees) provided the exertion in all but 2 instances. In these 2 cases a series of exacting "setting up" exercises during a 5-minute period were used. Before the activity, blood samples sufficient to yield the determinations considered below were taken from the finger tip of the subject. The data obtained from this preliminary group of "counts" constituted the normal condition of the red corpuscles of that individual. Immediately after the exercise (no interval allowed) a second sampling was obtained and additional ones were made every 15 minutes thereafter until a total of 8 had been recorded (Table 2).

Six determinations were made from each group of samples and were obtained in the following manner:

1. *Total Red Count.* The drop of blood from the finger tip was diluted with Hayem's solution in a U. S. certified pipette. After a

thorough mixing of the corpuscles by placing the pipette in an electric agitator, the number of erythrocytes in 160 small squares (2 chambers) was recorded.

TABLE 1.—THE SIGNIFICANCE OF THE DIFFERENCE BETWEEN THE DETERMINATIONS BEFORE AND AFTER ACTIVITY (CALCULATED FROM ORIGINAL DATA).

	Mean.	Standard deviation.	Coefficient of variation, per cent.	Probable error of mean.	Difference of means.	Probable error of difference of means.	Significance of difference.*
Total red count:							
Before	4,440,000	713,000	16	±75,000	550,000	±82,000	+
After	4,990,000	317,000	6.3	±34,000			
Hemoglobin, grams:							
Before	14.28	0.78	6.8	±0.08	0.35	±0.13	−
After	13.93	0.89	7.5	±0.10			
Volume, per cent:							
Before	39.8	2.4	6	±0.2	0.09	±0.04	−
After	40.7	3.2	7.8	±0.3			
Mean corpuscular hb., micromicrograms:							
Before	31.46	1.61	5.1	±0.17	2.75	±0.28	+
After	28.71	2.08	7.2	±0.22			
Mean corpuscular volume, c.μ							
Before	89.80	5.43	6	±0.59	7.85	±0.99	+
After	81.95	7.22	8.8	±0.79			
Mean corpuscular hb. concentration, per cent:							
Before	35.11	1.93	5.5	±0.21	0.04	±0.36	−
After	35.15	2.47	7	±0.27			

* "Unless a deviation is more than four times its probable error, there is no great reason for thinking it may not result from pure chance."[7]

2. *Total Hemoglobin.* The blood sample was drawn into a hemoglobin pipette and diluted with a 1 per cent solution of hydrochloric acid. After intervals of 20 minutes or more readings were made in a dark room with a Duboscq colorimeter provided with a Bausch and Lomb-Newcomer hemoglobin attachment. In all instances the values were read with light from an 8-inch Corning daylight lamp. The determinations expressed in grams per 100 cc. of blood were the averages of at least 5 readings of each sample. As these readings were too low, 2.48 gm. per 100 cc. were added, the correction figure having been obtained by previous comparison with the measurement of the hemoglobin content of blood by the van Slyke apparatus.

3. *Volume Percentage.* The blood was prepared for study in van Allen hematocrit tubes according to the methods suggested by that author.[2,3] A 1.3 per cent solution of sodium oxalate was used as the most satisfactory diluent. The tubes were sealed with padded rubber bands and then centrifuged at a speed of 4000 revolutions per minute (radius of arm, 7 cm.) until 2 consecutive readings made at 5-minute intervals yielded the same value. In every case the centrifuging continued for at least 30 minutes. The column of

packed erythrocytes was read in terms of the percentage of the total original column (*e. g.*, corpuscles 40 per cent of total volume of sample).

TABLE 2.—DATA FOR RED-CELL VALUES FOR THE 4 SERIES OF 10 EXPERIMENTS EACH, BEFORE AND AFTER A 2-MINUTE PERIOD OF HARD EXERCISE.

	Before activity.	After activity.	15 min.	30 min.	45 min.	60 min.	75 min.	90 min.
1. *Total Erythrocyte Counts (Millions).*								
Subject H	4.29	4.70	4.68	4.34	4.29	4.29	4.28	4.29
Subject K	4.67	5.17	4.99	4.71	4.66	4.64	4.65	4.65
Subject G	4.26	4.81	4.72	4.35	4.27	4.26	4.27	4.27
10 persons	4.54	5.32	4.90	4.64	4.57	4.54	4.53	4.53
Average (40 experiments)	4.44	5.00	4.82	4.51	4.45	4.43	4.43	4.44
2. *Total Hemoglobin (Grams).*								
Subject H	14.0	14.7	14.4	14.1	13.7	13.8	13.5	13.5
Subject K	14.3	14.4	14.2	14.2	14.3	14.2	14.3	14.2
Subject G	13.1	13.2	13.3	13.1	13.2	13.1	13.1	13.0
10 persons	14.4	14.9	14.7	14.4	14.4	14.3	14.4	14.4
Average	14.0	14.3	14.2	14.0	13.9	13.9	13.8	13.8
3. *Total Volume (Per cent).*								
Subject H	40.8	42.2	41.4	40.7	41.0	42.1	40.7	41.9
Subject K	41.0	42.2	41.9	40.9	41.3	41.1	41.4	42.2
Subject G	37.7	38.0	38.1	36.7	37.6	37.2	37.0	37.4
10 persons	39.8	40.6	40.0	39.3	39.2	39.6	39.4	39.6
Average	39.8	40.8	40.4	39.4	39.8	40.0	39.6	40.3
4. *Corpuscular Volume (Cubic Micra).*								
Subject H	95.0	89.9	88.6	93.9	95.5	98.2	94.9	97.6
Subject K	87.9	81.5	84.5	86.8	88.7	88.5	89.1	90.6
Subject G	88.4	78.9	80.8	84.2	88.0	87.2	86.5	87.6
10 persons	88.0	77.5	81.9	85.0	86.2	87.3	87.1	87.0
Average	89.8	82.0	84.0	87.5	89.6	90.3	89.4	90.7
5. *Corpuscular Hemoglobin (Micromicrograms).*								
Subject H	32.6	31.3	30.8	32.5	31.9	32.2	31.5	31.5
Subject K	30.6	27.9	28.5	30.2	30.7	30.6	30.8	30.5
Subject G	30.8	27.4	28.2	30.1	30.9	30.8	30.7	30.4
10 persons	31.7	28.0	30.0	31.0	31.5	31.5	31.8	31.8
Average	31.4	28.7	29.4	31.0	31.3	31.3	31.2	31.1
6. *Corpuscular Hemoglobin (Concentration, Per cent).*								
Subject H	34.3	34.8	34.8	34.6	34.3	32.8	33.2	32.2
Subject K	34.9	34.1	33.9	34.7	34.6	34.6	34.5	33.7
Subject G	34.8	34.7	34.9	35.7	35.1	35.2	35.4	34.8
10 persons	36.2	36.7	36.8	36.6	36.7	36.1	36.6	36.4
Average	35.1	35.1	35.1	35.4	35.2	34.7	34.9	34.3

4. *Mean Corpuscular Volume.* The average size of a red corpuscle was calculated by the use of Wintrobe's[4] formula:

$$\text{Corpuscular volume (cubic micra)} = \frac{\text{Volume of packed cells (cc. per 1000 cc.)}}{\text{Total red-cell count (millions per cu.mm.)}}$$

$$e.\,g.,\ \frac{400}{4.4} = 90.9$$

5. *Mean Corpuscular Hemoglobin.* The average amount of hemoglobin in a single cell was determined by using the formula employed by Wintrobe:[4]

$$\text{Corpuscular hb. (micromicrograms)} = \frac{\text{Total hb. (gm. per 1000 cc.)}}{\text{Total red-cell count (millions per cu.mm.)}}$$

$$e.\,g.,\ \frac{140}{4.4} = 31.8$$

6. *Mean Corpuscular Hemoglobin Concentration.* Since the proportion of hemoglobin in relation to other corpuscular contents was considered as important as the quantity in each cell this final set of calculations was made according to the following equation:[4]

$$\text{Corpuscular hb. concentration (in per cent value)} = \frac{\text{Total hb. (gm. per 100 cc.)} \times 100}{\text{Volume in cc. per 100 cc.}}$$

$$e.\,g.,\ \frac{1400}{40} = 35.0$$

Preliminary experiments were performed in each type of technique to ensure satisfactory accuracy in the accumulation of the data.[5,6]

Results. 1. *Total Red Count.* The pattern of the curve in Chart I showed marked increase in the number of erythrocytes immediately after exercise (average increase of 550,000 cells) and a gradual return to normal within a period of 30 to 45 minutes. In subject H, the second and third points were nearly alike and the maintenance of these high values was followed by a fairly abrupt drop to the normal level. Each separate experiment on this individual presented a picture of the same type. The series on subject G showed a tendency toward the same sort of pattern but, in general, it might be said that in subjects K, G and 10 persons there was no evidence of a plateau as in subject H, and the drop in total number was marked and progressive within the first 15 minutes after exercise (Table 2).

2. *Total Hemoglobin.* The amount of hemoglobin in the blood was slightly but not significantly increased by exercise (Chart I, Table 1). There was an early return to normal values. The hemoglobin content in the H series had a more decided rise immediately

after exercise and, unlike the other 30 experiments, dropped below normal and maintained itself at this lower level (Table 2).

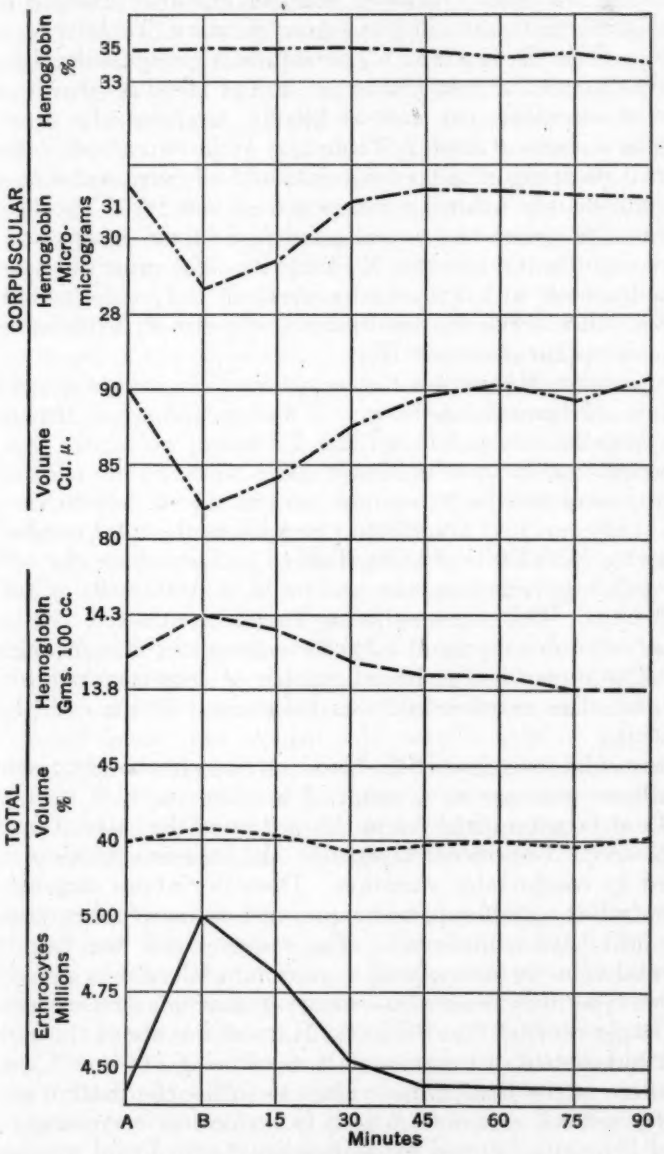

CHART I.—Composite curves, 40 experiments. The effect of 2-minute periods of exercise on red-cell values. *A*, before exercise; *B*, immediately after exercise.

3. *Volume Percentage.* The volume percentage changed but little (Chart I, Table 1). Separate experiments exhibited some variations in results and occasionally actual drops in volume percentage occurred following activity; however, in 31 of the 40 cases there was a slight increase or an unchanged condition.

4. *Corpuscular Volume.* The estimated corpuscular volume (the total cell volume per unit of blood divided by the total number of cells per unit of blood) dropped immediately after exercise and regained its normal values in ¾ to 1 hour (Chart I, Table 1).

5. *Corpuscular Hemoglobin.* The estimated corpuscular hemoglobin (the amount of hemoglobin per unit of blood divided by the number of corpuscles per unit of blood) paralleled the drop in corpuscular volume (Chart I, Table 1). Without exception there was a real decrease in the average amount of corpuscular hemoglobin immediately following the period of activity. The lowest value was attained at the second point in 3 of the groups and at the third point in the series on H (Table 2). The return to normal was simultaneous with a similar recovery of the total number of corpuscles and was likewise maintained to the end of the experiment with the exception of subject H.

6. *Corpuscular Hemoglobin Concentration.* The constancy of the proportion of hemoglobin in a cell during and after strenuous activity is well shown in Chart I and Table 1.

Discussion. As in most of the previous work on the effect of a short period of strenuous exercise on red blood corpuscles, the present study revealed a significant increase in the total number of erythrocytes (550,000 ± 82,000, Table 1). Sometimes the actual change following exertion was as low as 130,000 cells (Case 7, original data). This slight variation may be contrasted with such a marked response as a rise of 1,200,000 corpuscles (Case 36, original data). The return to the initial number of cells occurred within 45 minutes after exertion and was maintained to the end of the experiment.

The hemoglobin content of the blood, on the other hand, presented no significant increase as a result of exercise (0.35 ± 0.13 gm., Table 1), although a slight rise in the pattern of the curve (Chart I) could be seen. Considered separately, the experiments were characterized by considerable variation. These deviations may be due to uncontrolled variables in technique, such as many other workers in this field have experienced. The second count was less than the normal value in 9 cases with a maximum fall of 0.48 gm. (Case 13). One experiment showed no change at all after exercise (Case 7). In 30 (75 per cent) of the studies the B count was above the normal hemoglobin content, the maximum increase being 2.06 gm. (Case 5). This failure of the hemoglobin values to follow the pattern of the curve for red-cell numbers (Chart I) seemed to corroborate the work of Schmaltz (quoted by Willebrand)[8] who found no change in specific gravity or hemoglobin content after 10 minutes of hard exercise, and of Mitchell[9] who obtained inconstant increase and one not proportionate to the rise in red corpuscles. On the other hand, Boothby and Berry,[10] Schneider and Havens[11] and Broun[12] calculated increases of 8.3 per cent, 3.5 per cent to 10.9 per cent,

and 8.5 per cent respectively. Orias,[13] working with somewhat different conditions, concluded that there was a real drop in the hemoglobin in his subjects after 15 days of intense exercise and a gradual return to a normal content in the blood within a period of 4 to 6 days following the cessation of exertion. Since the length of activity was so great he was probably justified in explaining this decrease as due to red cell destruction. A similar conclusion was reached by Broun[14] upon study of the blood picture of dogs after they had been subjected to prolonged periods of activity.

Although the total hemoglobin content did not change significantly in these studies, there was a real decrease in the amount of hemoglobin in the cells after exercise (2.75 ± 0.28 micromicrograms; Chart I, Table 1). These data lend weight to the suggestion of Mitchell[9] that incoming cells with less hemoglobin value than normally found in the peripheral circulation accounted for the disproportionate and highly variable response of the hemoglobin content. Accompanying this decrease in corpuscular hemoglobin there was no real alteration in the amount of hemoglobin in each cell in proportion to its volume. The difference in the average corpuscular concentration in 40 experiments before and after exercise was found to be less than its probable error (Table 1).

The volume percentage as determined by the hematocrit method with a small amount of blood showed no significant change which could be attributed to the effects of exercise (Table 1). With the real increase in the number of cells (average 550,000) there was only a slight increase in the total volume (0.09 ± 0.04 per cent). However, with the same method of volume determination, Smith and Prest[6] found that women with total counts of 420,000 cells less than the normal average also had about 4 per cent lower total volumes. If a proportional increase in volume had accompanied the rise in the number of cells in these experiments, it should have been of sufficient magnitude to have been measured by the method employed.

In contrast to these findings are those obtained by previous investigators. Edgecombe[15] showed that with a fall in amount of hemoglobin was a rise in the percentage volume of erythrocytes. The latter was augmented considerably when profuse perspiration occurred. Broun,[12] Scheunert and Müller,[16] Scheunert and Krzywanek, [17a, 17b, 18] Krzywanek and Arnold,[19] and Arnold and Krzywanek[20] obtained real increases in volume percentage. Arnold and Krzywanek furthermore noted that the increase in volume was not as great in man as in experimental animals.

Though the volume percentage did not change, the decrease in the average corpuscular volume after exercise was found to be real (7.85 ± 0.99 cubic micra; Chart I, Table 1). Price-Jones[21,22] has emphasized the increase in cellular diameter following vigorous exercise (running up and down 6 flights of stairs 3 times). He

associated the increase with a diminution in alkalinity of the blood. Wiechmann and Schurmeyer[23] verified these observations on cells during muscular fatigue. Broun[12] stated that his data were too few to give figures on the average cell size, but he believed they tended to confirm the work of Price-Jones. On the other hand, Scheunert and Krzywanek[17a, 17b] stated that the volume of a single cell remained constant during rest and activity. Dryerre, *et al.*,[24] found no real difference between the mean diameters of erythrocytes before and after violent exercise, although from their tables the average for the readings taken after exercise was slightly less than the one before. Ponder and Saslow[25] reported that they obtained no evidence of an increase in diameter of the average corpuscle after exercise (running down 6 flights of stairs and back again) that could not be accounted for by the error of the method. When their determinations for 25 persons at rest and after exercise were averaged, the mean for those after exercise was 0.04 μ less than the one before.

In order to test the decrease in cell volume in this series of experiments as found by the division of the total volume by the total cell count, 5 sets of slides were made for the measurement of cells from dried films. Cells magnified 1300 times were projected by means of the euscope and measured directly with very fine compasses on a transparent protractor divided into $\frac{1}{2}$ mm. parts (method of Sauder and Toomey).[26] The ground glass screen was lighted evenly so that almost all the cells could be measured (2 diameters for each of 200 cells on 5 slides before exercise and 5 slides after exercise). The results were as follows:

TABLE 3.—EFFECT OF EXERCISE ON DIAMETER OF RED CELLS.

	Before exercise, micra.	After exercise, micra.
1 (Average 400 diameters, 200 cells)	7.94	7.78
2 " " "	7.92	7.88
3 " " "	7.67	7.69
4 " " "	7.64	7.68
5 " " "	7.60	7.65
Average (from 2000 diameters, 1000 cells)	7.78	7.76

The difference (0.02 μ) between the two means was found to be about equal to its probable error and therefore not significant. These data confirmed those of Dryerre, *et al.*,[24] and Ponder and Saslow[25] in that the variation came within the limit of error of the method and could not be proved real. The measurement of dried cells is admittedly inaccurate, but even so the tendency was toward cells of less diameter, when all data were averaged, rather than greater, as indicated by Price-Jones. If, as Haden[27] noted, a change in diameter of 1μ caused a variation of 44 per cent in cell volume, then a difference of about 9 per cent in volume as found in these studies might well be difficult to detect in dried cells.

Six possible causes for the increase in the number of erythrocytes have been outlined by Hawk:[28] (1) production of new cells; (2) concentration of blood through increased urine formation and copious perspiration; (3) concentration of blood through vasomotor contraction and rise in blood pressure; (4) concentration of the blood through evaporation in the lungs; (5) sudden passage into the circulating blood of a large number of cells lying in various parts of the body and inactive before the time of muscular exercise; (6) passage of fluid from the blood to the active muscles. Long continued exercise may produce effects depending on these and other factors, but the initial increase in corpuscles in the peripheral blood immediately after 2-minute periods of hard exercise as described in these studies would seem to be due largely to a sudden shower of cells from reservoirs, principally the spleen, in other parts of the body, Mitchell,[9] Edgecombe,[15] Hawk,[28] Broun,[12] Scheunert and Müller,[16] Scheunert and Krzywanek,[17a, 17b, 18] Abderhalden and Roske,[29] Barcroft and Poole,[30] Barcroft and Stevens.[31] No perspiration was noted in the present experiments except in the 5 series where only the dried smears were made for the measurement of cells. There was also no definite change in the number of reticulocytes. The rapidity of the response of the erythrocytes after short periods of vigorous exercise, the lack of sensible perspiration, and the failure to demonstrate an increase in new cells would be indirect evidence in confirmation of the statement of Barcroft and Poole[30] that "there seems to be no doubt, however, that the spleen does play a considerable rôle in the increment of corpuscles during asphyxia and during exercise, even though it may not be responsible for the whole phenomenon."

Conclusions. 1. Two-minute periods of strenuous exercise produced a transient increase in the total number of red corpuscles per cubic millimeter in the peripheral blood stream.

2. This short but severe exertion failed to alter significantly the total amount of hemoglobin or the volume percentage of erythrocytes.

3. A drop occurred in the estimated mean corpuscular volume and mean corpuscular hemoglobin immediately after exercise, suggesting that cells were present smaller in size and containing less hemoglobin than those normally circulating in the capillary beds of the body surface.

4. The smaller amount of hemoglobin was correlated with the decreased volume of the corpuscles, so that the proportion of hemoglobin to other corpuscular contents remained relatively constant during rest and exercise.

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CONTACT DERMATITIS (VENENATA).

DISTRIBUTION AND IMPORTANCE OF THE HELENIUMS AS A CAUSE OF CONTACT DERMATITIS IN THE UNITED STATES.

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DURING the past two years we have found Helenium microcephalum D. C. to be a rather common cause of contact dermatitis (venenata). Weber[1] names Helenium autumnale in his list of cutaneous irritants. Andrews[2] states that the heleniums (the sneeze weed family) belong to the group of plants which are known to cause systemic reaction following contact. We have found no other reference concerning the helenium family in medical literature. Since we have seen a number of cases of severe dermatitis due to the heleniums, and knowing that the plant is very abundant in the Southwest, we are led to believe that the helenium family may be of considerable importance in the cause of dermatitis through many sections of this country, which accounts for our detailed study of the distribution of this plant throughout the entire United States.

Distribution. The finding of a number of severe cases of dermatitis venenata due to the heleniums caused us to investigate every section of our state, as well as New Mexico, Texas, Kansas and Arkansas, from the standpoint of the abundance of the helenium plant. We found the plant very abundant along the roadsides and in the poorly drained areas of the prairies of the panhandle of Texas and of many sections of New Mexico, western Kansas and western Oklahoma. Occasionally plants were found in eastern Oklahoma and western Arkansas.

Questionnaires were sent to the professors of botany of the universities and agricultural colleges in every state in the Union. A detailed reply from all but 6 states was obtained. Information concerning the plant in these states was obtained from the foresters.

Information received from the professor of botany, University of Kansas, stated that the plant is fairly commonly found in the eastern section of the state. The professor of botany, University of Arkansas, reported the plant rather generally distributed but nowhere very abundant in the state. From Louisiana a report came that it is very abundant along the roadsides and waste places.

Nevada, Arizona, Idaho, California and Utah all report one or more species of helenium to be moderately common and fairly well distributed throughout their states. We were interested in the reports which came from Oregon and Washington. The professor of botany of the University of Oregon stated that "hundreds of acres of the Helenium autumnale grow along the Columbia River, less elsewhere." He reports a number of other varieties in the state. Likewise information from the professor of botany of the University of Washington is similar in character. Wyoming reports show that the plant is fairly abundant along the Platte River. In Colorado it occurs but rarely. In Montana, North and South Dakotas and Nebraska information was given us that it is common in low places and fairly well distributed throughout these states. In Minnesota the plant is abundant as far north as the Twin Cities. In Wisconsin it occurs but rarely.

Information received shows the plant to be quite well distributed and in some places very abundant in Ohio, Indiana and Illinois. Charles C. Deam, Research Forester for the State of Indiana, states as follows:

> "Helenium autumnale is a common plant in all parts of Indiana. . . It is a denizen of low ground and is most frequently found in low open fields in wet land and along ditches. It rarely grows in thick colonies and is usually found as single plants here and there, but sometimes it grows fairly thick. On the contrary, Helenium nudiflorum is usually a common plant where it is found and grows in large colonies. I have seen it by acres, usually in waste land or pasture fields. All species of the genus are avoided by stock and are reputed to be poisonous to them. . . . This month (October, 1931) I found a pasture of about 3 acres of Helenium tenuifolium. . . . The species was almost a pure stand and stock did not touch it."

A report from the Virginia Polytechnic Institute shows that the plant is quite widespread in Virginia along the Blue Ridge and Allegheny Mountains. The professor of botany at Charlottesville, Va., reported it to be fairly common, but rather abundant along the southwestern mountains of the state, and said that it was found in fair abundance around Richmond. From our reports we find it fairly common along the streams in New York and moderately abundant in Maryland, Delaware and New Jersey. The professor of botany at the Massachusetts Agricultural College at Amherst advises us that the plant is common in Berkshire County but rare in other sections of the state. It is found in Connecticut, Rhode Island and Maine but not abundant in these three states.

All states south of the Ohio River and east of the Mississippi, except Florida, reported one or more species of the heleniums to be common and fairly widely distributed. It rarely occurs in Florida.

A great many botanists reported that Helenium autumnale was common. After studying the helenium family in detail during the

last few months, and after a conference with the Assistant Director of the New York Botanical Garden, Marshall A. Howe,[3] we feel that many of the botanists in reporting Helenium autumnale were possibly referring to some other species, as there are many species.

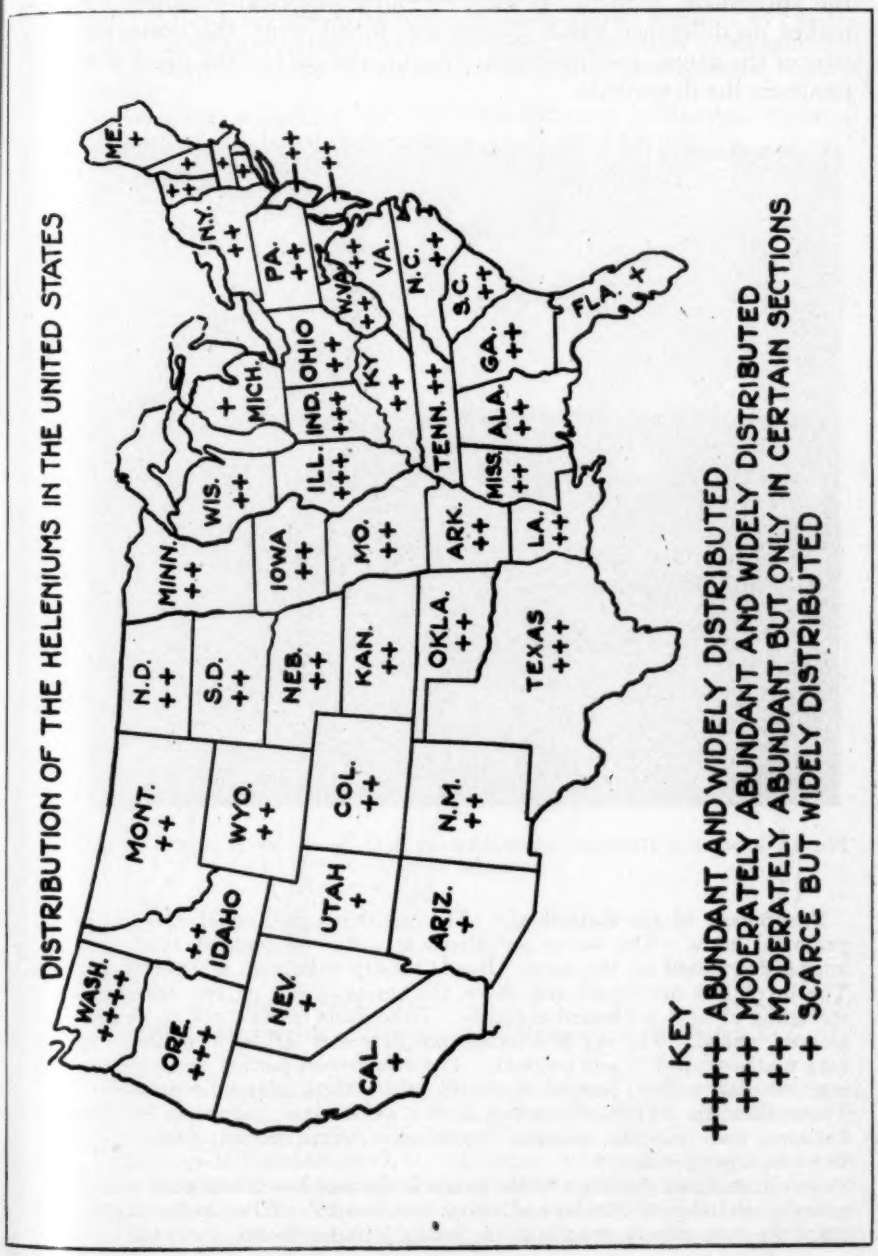

FIG. 1.—Map showing distribution of the heleniums in the United States. More than 50 per cent of the states show the plant to be fairly abundant and widely distributed.

Helenium autumnale is very common in the eastern third of the United States. In the midcentral territory Helenium microcephalum D. C. is common. In the western section of our country Helenium montanum and Helenium nudiflorum are more common and the autumnale, if found, is rare. From a practical standpoint it makes no difference which species was found, since the characteristic of the genus is an oleoresin, which is the part of the plant that produces the dermatitis.

FIG. 2.—A patch of Helenium microcephalum D. C. (sneeze weed) on the plains of western Texas.

The Botany of the Heleniums.[4] The heleniums are annual, biennial or perennial herbs. The leaves are alternate, entire or toothed, often prolonged downward on the stem. Heads mostly with rays and peduncled. The involucres are broad and short, the bracts in one or two series and spreading or bent backward abruptly. Receptacle convex, oblong or subglobose, naked. The ray flowers are pistillate and fertile, or neutral, the rays wedge-shaped, 3 to 5 toothed. The disk flowers perfect, fruit-producing, corollas yellow, purple or brown, their teeth glandular-pubescent. The anthers are 2-toothed or arrow-shaped at the base; stigmas of the disk flattened and truncate; achenes broadened upward, ribbed; pappus of 5 to 8 awn-tipped scales.

An outstanding character of the genus is the presence of bitter, aromatic, resinous globules on the leaves, stems and flowers. When collecting the plant the resin adheres readily to the hands. Under the hand lens the resin

appears as minute globules of oil, very thickly distributed over the surface of the plant.

Helenium Autumnale. A perennial with a more or less pubescent stem, narrowly winged by the decurrent bases of the leaves, 2 to 6 feet high. Leaves are oblong, lanceolate or ovate-lanceolate, 2 to 5 inches long, ¼ to 2 inches wide, prominently toothed, sessile (attached to stem without stalk). Heads are numerous, borne on stalks of great length, 1 to 2 inches broad, including rays; rays, 10 to 18, drooping, bright yellow; disks spherical.

The stem, leaves and flowers are sprinkled with bitter aromatic resinous globules.

This species is known to hybridize with Helenium nudiflorum. Many of the specimens collected show evidence of this hybridization.

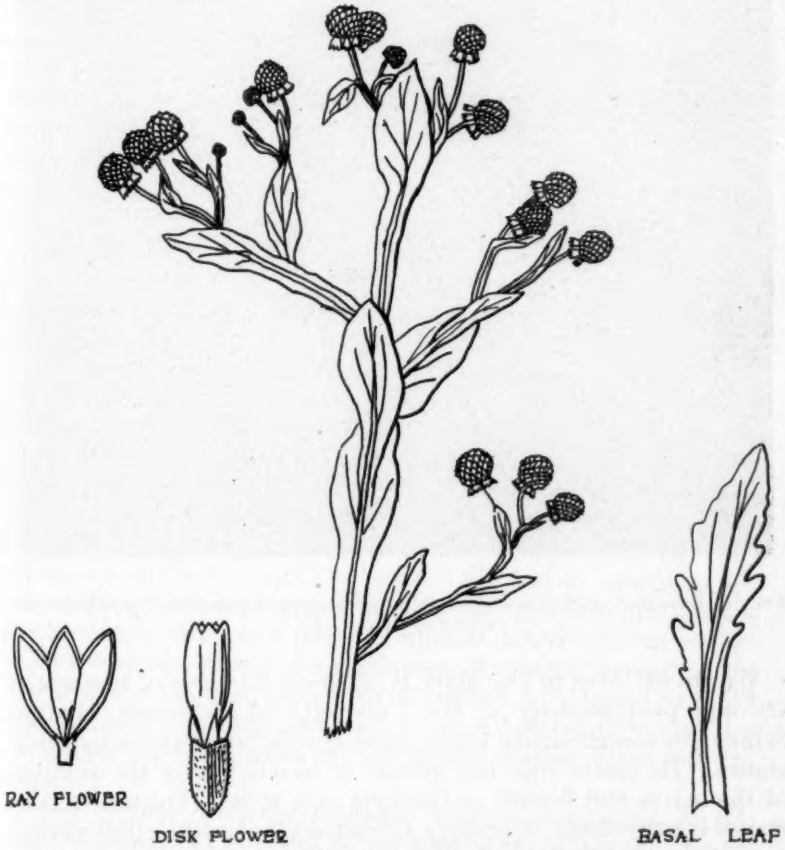

FIG. 3.—Drawing showing the botany of Helenium microcephalum D. C.

This species grows in low, usually poorly drained prairies and meadows; blooms from July to October. It is widely distributed from Quebec to Florida, Manitoba, Oregon, Oklahoma, Texas and Arizona.

Helenium Microcephalum D. C. Helenium microcephalum D. C. (sneeze weed or bitterweed) is an annual leafy plant, 1 to 2½ feet high, with winged angular stems. The leaves are simple, the blades oblong to lanceolate, 3 to 8 cm. long, clasping the stem and continuing down the stem fully half

the length of the blade, those of the lower leaves often toothed. Flowers are 5 to 6 mm. in diameter, disk globular, the rays 3 to 5 mm. long, yellow, wedge-shaped, folded against the stems.

The plant grows in moist soil, depressions that are locally called hog-wallows, and banks of small streams.

It is found growing in southern Oklahoma, Texas and adjacent Mexico.

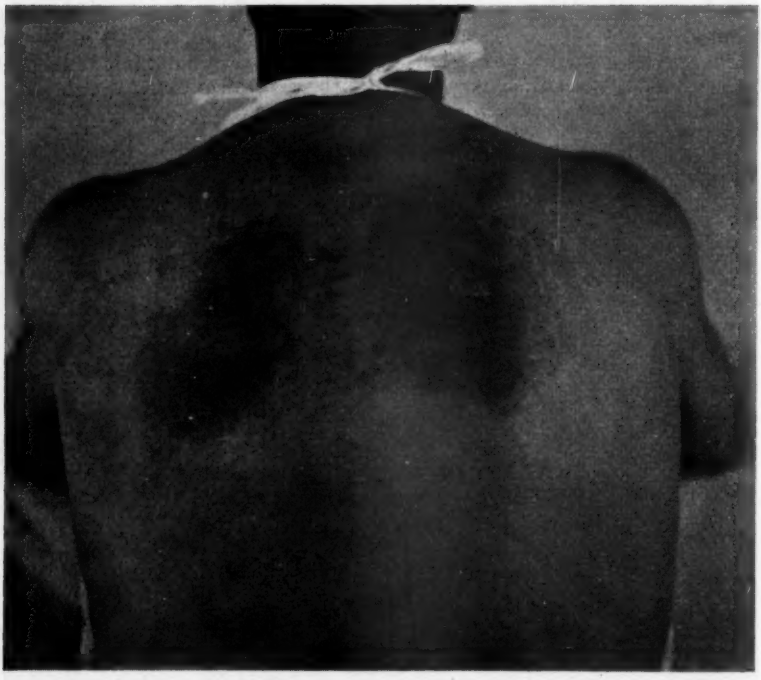

FIG. 4.—Results of patch test 24 hours after application of ground leaves of Helenium microcephalum D. C.

We are indebted to Dr. Mark R. Everett, professor of biochemistry and pharmacology at the University of Oklahoma Medical School, for a preliminary report upon the nature of the active substance. He states that the irritant is secreted upon the surfaces of the leaves and flowers in the form of a resin. The active substance is nonvolatile, is entirely extracted by absolute ethyl alcohol at room temperature, is also soluble in benzene or ether, but relatively insoluble in petroleum ether or water. Further chemical studies on the exact nature of the irritant are being made by Dr. Everett.

Skin Test Findings. Patch tests were run with the ground-up leaves, flowering tops, the oleoresin as a whole, and the various fractions. We were very much interested in the fact that of all the substances we have ever used in patch testing the oleoresinous

material from the helenium plant produced the most marked local and systemic symptoms. A 10 per cent solution of the oleoresinous material in olive oil was used in doing the patch tests. The absolute ethyl alcohol fraction gave by far the most marked reactions. Some patients would obtain not only a marked local reaction in the course of a few hours, but would also have systemic reactions manifested by abdominal cramps, with diarrhea. We mention this to show the marked toxicity of the resinous material. Patients should be carefully watched following testing, as we have found systemic reactions not uncommon. For patch testing a 10 per cent solution of the ground-up leaves or heads, or the extracted oleoresin in olive oil, may be used. (Careful) controls on nonsensitive patients should always be made.

Importance of the Heleniums as a Cause of Contact Dermatitis. During the past 2 years we have seen several cases of contact dermatitis due to Helenium microcephalum D. C. Two of these cases have been recently reported in detail by one of us.[5] As we review a number of cases of dermatitis of unknown origin whom we saw before we were testing with the oleoresin of helenium, we feel confident that a number of them were due to contact with this plant. Since in our clinic we deal only with the allergic phase of dermatology, the number of cases of contact dermatitis who come to us would naturally be comparatively small compared with those who apply to the dermatologist for relief of their symptoms. We feel, therefore, since we have seen a number of cases during the last 2 years the cause of which we could trace to one of the heleniums, that evidently the dermatologists in the Southwest have also seen a large number of similar cases. We find on personal interview with some of the leading dermatologists in this section that they are entirely unfamiliar with the plant. We find in careful review of the medical literature during the past 10 years that the plant is mentioned only twice as a possible cause of dermatitis, but we can find no record of a report of a single case of contact dermatitis, the cause of which has been proven to be contact with helenium. We would naturally conclude that many cases of contact dermatitis due to helenium are being unrecognized by the dermatologist and the allergist.

In our reports from the botanists from various states of this country we find that in about 50 per cent of the states the plant is profuse and widely distributed; in about 35 per cent it is fairly abundant and widely distributed, but it occurs in all the states. The habitat of the plant is the roadside, especially at the side of the ditch along the road. It occurs in the poorly drained areas of the semiarid sections of the United States. Frequently the plants are individual and do not grow close together. We have observed them around barn lots and in the wheat fields as individual plants, but many places where there is a wet area there will be from a quarter

acre to several acres of the plant growing very thickly. Some of the varieties of helenium are described in various garden books and are used as borders on the lawn. The possibility of contact with the plant is (fairly) great; for example, those who work on the public roads, the farmer, the telegraph and telephone lineman, the man who works in the wheat field, the rancher, the hunter, the oil-field worker and in some cases the women who work with their shrubbery, certainly have adequate contact with the plant. Coca[6] states that, differing from the usual allergic individual who is subject to the atopic hereditary influence, about 70 per cent of the white race may have contact dermatitis. In other words, nearly three-fourths of those who have adequate contact with the heleniums have an excellent opportunity to develop a dermatitis.

As previously stated, there are many varieties of the helenium. In some sections of the country Helenium autumnale grows, while in other sections Helenium microcephalum D. C., etc., but since the oleoresin is the characteristic of the genus we are not primarily concerned with the individual species. Since one of the species of the helenium grows in every state in the Union, and in the majority of the states is widely distributed and fairly abundant, the number of people who come in intimate contact with the plant is evidently very large. Since about 70 per cent of those who come in contact have a possibility of developing a dermatitis, surely this plant is an important factor in the United States in the cause of contact dermatitis. It seems that it is frequently overlooked as an etiologic factor.

The cases of dermatitis due to helenium we have seen have all come from Oklahoma, New Mexico, Texas and Kansas, and our personal observation of the plant has been in these states. Knowing what we do about the abundance of this plant in these states, and realizing the severity of its toxicity, we naturally became very much interested in the plant and feel that we are justified in making a detailed report.

Summary. 1. Very little concerning the helenium family can be found in medical literature.

2. Helenium microcephalum D. C. is an important etiologic factor in contact dermatitis (venenata) in the Southwest.

3. One or more species of the helenium family grow in every state in the Union.

4. The irritating substance is an oleoresin. It is soluble in absolute alcohol, benzene or ether and relatively insoluble in water.

5. Since the characteristic of the genus is an oleoresin, any species should be important from the standpoint of contact dermatitis.

6. Patch tests should be made with great care because a systemic reaction may occur, manifesting itself by abdominal cramps, diarrhea, conjunctivitis and headache.

7. The widespread distribution of the heleniums and their habitat affords adequate contact for the development of a specific sensitization.

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THE RELATION OF NEOCINCHOPHEN TO THE QUESTION OF CINCHOPHEN TOXICITY.*

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Phenylcinchoninic acid (cinchophen) was discovered in 1887 by Doebner and Gieseke.[1] In 1908 Nicolaier and Dohrn[2] described its therapeutic action, and since that time it has been extensively used as a therapeutic agent. In 1913 Phillips[3] described idiosyncratic skin reactions to cinchophen; and in 1922 Schroeder[4] called attention to the toxic action of cinchophen. In 1923 Worster-Drought[5] reported a case developing urticaria and jaundice after the use of cinchophen. Since that time clinicians have become increasingly more cautious in the use not only of this drug but also of its derivatives, the most important of which is neocinchophen.

In 1929 Reichle[6] collected and reported 49 cases of toxic cirrhosis of the liver due to cinchophen or its derivatives. Ten of these patients died. In these cases the dose necessary to produce symptoms varied from 15 grains to 4000 grains administered over various periods. In 1930 Rabinowitz[7] collected 50 cases, 25 of which died and autopsies were performed on 20. During the discussion of his paper 6 more cases were reported, 5 of which died. It is interesting

* This research was aided in part by a grant from Mrs. John L. Gevin in support of surgical research.

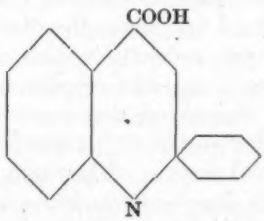
that none of the deaths were due to neocinchophen alone. In 1925 Cabot[8] reported a case of acute yellow atrophy said to be due to a course of "Weldona," a proprietary preparation which was supposed to contain a carbonate, cascara sagrada and neocinchophen. Grolnick[9] also reported a case of toxic hepatitis due to "Weldona," symptoms having developed after 12 tablets were taken, with recovery of the patient. There is, however, considerable doubt as to the contents of "Weldona." In 1924 the American Medical Association published the results of its analysis of these large lavender tablets which were found to contain sodium salicylate and an unidentified vegetable extract. No alkaloids, iodids, acetylsalicylic acid, phenyl salicylate, or neocinchophen were found. Similarly the Health Bureau of Rochester, N. Y. made tests on "Weldona" in 1925. In 1926 the Chemical Laboratory of the American Medical Association completed another analysis of "Weldona" with the same result. Accordingly the *Journal of the American Medical Association* concluded,[10] "It seems evident from these various analyses, made over a period of years, that 'Weldona,' like so many other patent medicines, is a name rather than a thing—while the name has remained constant the composition has varied." Walker[11] has reported 2 cases of toxic hepatitis, both of which died.

Parsons and Harding added 4 more fatal cases.[12] In a survey issued by the Calco Chemical Company[13] in October, 1931, 100 cases of suspected poisoning from phenylcinchoninic acid or its derivatives throughout the world since 1913 were reported. Of these 36 died, a large proportion of which were proven to be acute yellow atrophy at autopsy. Based upon these late and rather complete figures, however, a rough computation of the incidence of fatal intoxication is about 1 to 500,000 patients for this country. In May, 1931, Ross[14] reported 5 cases of acute hepatitis, 3 of which died and gave proof of the diagnosis at autopsy. One of these had taken tolysin intermittently for a period of 2 months, exact dose unknown. Prior to this there had appeared in the literature no authentic occurrence of a fatality due to neocinchophen. This case has been investigated but, because of the difficulty of obtaining complete facts at a labor camp in Canada where the administration occurred, the question of substitution cannot be settled definitely. The patient claimed to have purchased tolysin for self-medication but at the time of medical attendance none of the drug could be found to ascertain whether substitution had taken place. In July, 1931, Sherwood and Sherwood[15] reported a case of acute hepatitis due to cinchophen with recovery.

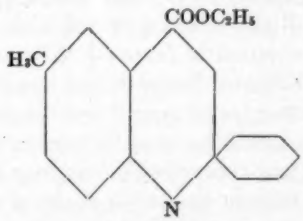
The wide interest aroused in the medical profession by the cited publications led the author to the further studies reported herewith. Although various observers have occasionally noted the lesser toxicity of neocinchophen, it appeared to the author that the degree of difference in toxicity has neither been sufficiently studied nor

adequately described. Louise Rotter[16] was the first to show the profound pharmacologic differences engendered by transposition or multiplication of side-chains upon the quinolin nucleus. Briefly summarized, it is impossible to predict toxicity from the apparent similarity of structural formulæ. These differences in toxicity have been attributed to various factors. Neocinchophen has been thought to be absorbed more slowly and to be less irritating to the kidneys. Hanzlik reported[17] 10 years ago that cinchophen sometimes produced albuminuria and a diminished phthalein output. Furth and Kuh,[18] however, state that tolysin is absorbed as completely as is cinchophen but somewhat more slowly. They performed most extensive experiments upon rabbits, dogs and humans, and from their work reached a conclusion which alters the older theories of physiologic chemistry, namely, that tolysin is absorbed by the intestinal mucosa without first undergoing any saponification. On the contrary, Hanzlik[19] in 1926 had postulated that the advantage of neocinchophen over the salicylates and cinchophen (relative absence of side-actions) was secured at the expense of poor solubility and absorbability of the neocinchophen. He concluded that therefore greater doses of neocinchophen must be taken to be effective, and that its apparent therapeutic advantage thus becomes less and the economic disadvantage to the patient becomes greater.

The respective structural formulæ of cinchophen and neocinchophen are shown below, and it will be noted that whereas cinchophen is an acid, neocinchophen is an organic *ester*, not of *cinchophen*, but of paramethylphenylcinchoninic acid.



Cinchophen



Neocinchophen

Once absorbed, the actions of these drugs have been assumed to be similar. The earliest and most important action noted was to increase the urinary output of uric acid. Probably this has occasioned more discussion than any other chemical subject in medicine. It is needless to enter into the controversy here, since it has not been disputed that this effect, whatever its cause, does occur. Subsequent to such clinical demonstrations it was discovered that these drugs were excellent antipyretics and analgesics and seemed to exert a semispecific action, so far as pain and disability were concerned, upon acute and chronic inflammatory processes of the bones, joints and tendons. Contemporaneously with the clinical studies,

pharmacologists in Germany were not idle in the wider investigation of these chemicals. Mendel[20] demonstrated paralysis of the ameboid movements of the leukocytes, followed by complete disintegration of their nuclei after the injection of sodium atophan into the thoracic lymph sac. From these results he assumed that the increase in uric acid elimination was due to leukocytic destruction *in vivo*, with the consequent release of large amounts of nucleoprotein into the blood stream. Starkenstein[21] later attempted to refute the conclusion of Mendel by stating, "The paralyzing action of atophan on the leukocytes explains, it is true, the depressing effect of this substance on inflammation, but the effect of atophan on purin metabolism is not an action on metabolism but an influence upon uric acid excretion." This view is generally accepted today. Dohrn[22] claimed that a slight leukocytosis followed the ingestion of atophan during the ensuing 4 or 5 hours and subsided within 24 hours. From these data he believed that leukocytic destruction played no part in the increase in uric acid elimination. We have been unable to obtain any increase in leukocytes after the ingestion of 30 grains of neocinchophen. It is a generally accepted hypothesis that this group of drugs increases renal permeability to uric acid, and Graham[23] believes that cinchophen at least facilitates the transport of uric acid to the blood from the tissue fluids and sodium biurate deposits. Griesbach[24] suggests that cinchophen tends to check the storage of uric acid in the tissues; and according to Starkenstein[25] it may inhibit purin metabolism.

Any attempt to review the entire literature on the value of neocinchophen is beyond the scope of this paper. Suffice it to say that Pulay[26] found it valuable in cases of urticaria; Bendix[27] used it in rheumatic fever; Jokl[28] used it in polyarthritis; Chace, Myers and Killian[29] found it the drug of choice in cases of suspected renal irritation; and many others similarly employed this ester. Barbour, Lozinsky and Clements[30] in 1923 reported 41 patients whom they had treated with varying amounts of tolysin. They concluded that tolysin appeared to be a very safe drug and could be administered more continuously than salicylates and in larger doses. Two of their patients received 450 grains within 8 days without any untoward symptoms. Boots and Miller[31] treated 20 rheumatic fever patients with tolysin. They compared these effects with those of sodium salicylate. In only 1 case did neocinchophen seem more toxic to the kidneys than sodium salicylate. The study seemed to show, however, that symptoms and signs of toxicity similar in character to those of salicylism occurred with full therapeutic doses of neocinchophen. Five of the 20 patients were free from symptoms of toxicity such as nausea, renal irritation, vomiting, or urticaria. They concluded that the symptoms of toxicity were not so marked in neocinchophen as in the case of the salicylates. Poynton,[32] in Great Britain, was favorably impressed with this ester.

The literature is replete with writers' impressions that their patients did not always tolerate cinchophen well. Chace and Fine[33] 17 years ago noticed that their patients were upset by it and that it could be taken only when well diluted with water or in conjunction with bicarbonate of soda. Occasionally patients have been seen who have an idiosyncrasy to the drug such that a very small dose will produce toxic symptoms. Evans and Spence[34] in Great Britain collected 3 cases, 1 of which had a family history of idiosyncrasy to the drug. In one instance cinchophen would produce an attack of gout.

It has been noticed that certain individuals react in an abnormal manner either to derivatives of the quinolin nucleus or to other derivatives of coal tar. Accordingly many clinicians in administering these drugs have deemed it wise to give small initial doses for the purpose of testing the patient's tolerance to the drug employed. Rabinowitz,[7] however, says that these precautions even when coupled with intermittent dosage often do no good. He contends that certain individuals are predisposed to hepatitis, particularly those with gall bladder disease, hepatic cirrhosis, chronic alcoholism, chronic nephritis, etc. Those who have in the past suffered from liver diseases associated with jaundice; those who have had eclamptic difficulty with pregnancy; and those showing other evidences of cinchophen intolerance, are apparently especially so predisposed. The drug appears particularly dangerous in states of hepatic damage accompanying starvation, malnutrition, cachexia, chronic infection and tonsillectomy, and in conditions favoring decreased glycogen content of the liver cells. Sensitization of the liver to protein by injection, ingestion or trauma renders the liver more susceptible to the toxic damage of cinchophen.

According to Brugsch and Horsters[35] cinchophen directly stimulates the bile-forming cells and so causes an actual increased secretion of bile. In patients with biliary fistula an increased flow of bile from 200 to 300 per cent was observed. Stransky[36] was unable to confirm these observations, but Grunenberg[37] and others have reported an increase in bile in the duodenal contents as the result of administration of cinchophen to healthy individuals and patients suffering from catarrhal jaundice. Brugsch[38] even maintains that there is no question of cinchophen being a liver poison when given in the usual doses, unless the patient has been on a carbohydrate-poor diet, and as a result has a poor glycogen reserve in the liver. He is so sure of the innocence of the drug that he uses it for the treatment of jaundice in subacute atrophy of the liver. Taubmann[39] states that cinchophen is excreted in the bile and inhibits carbohydrate digestion, and does therefore favor decreased liver glycogen storage.

The study of the physiologic chemistry and clinical pathology of cinchophen and oxycinchophen, recently published by Lichtman,[40] makes some illuminating comments upon the so-called hepatotoxic

action of cinchophen. He says in part, "There is evidence, however, that a single or even repeated standard test doses of 0.45 gm. are not toxic, even in the presence of severe damage of the liver. Studies were made on a patient with degeneration of the liver attributed to the ingestion some time before of approximately 18 gm. of cinchophen in a period of 18 days. . . . Thus in this case ascribed to the hepatotoxic action of cinchophen, 3 doses of 0.45 gm. of this substance given at intervals of approximately a week had no toxic action and did not delay clinical and functional recovery. . . . Similar observations have been made in all the cases of disease of the liver that have been studied. Thus far no instance of untoward effects attributable to the cinchophen employed in the test has been countered. . . . In fact, in many instances, a decrease in the intensity of the jaundice is noted on the day following the test, which may be due to the choleretic action of the drug."

The cause of the toxicity of cinchophen has been variously discussed by Rotter,[41] Willcox,[42] Sollmann,[43] Sherwood,[15] Crawford,[44] and others. The idea variously exploited that the oxidation of the quinolin nucleus produces highly toxic nitro compounds is very improbable. It is practically exploded by the work of Lichtman above referred to, which shows the oxidation products of cinchophen; and by the work of Furth and Kuh.[18] No explanation at present exists for the toxicity of cinchophen except hypothesis. The most likely and generally accepted hypothesis is that phenylcinchoninic acid, in the presence of certain predisposing conditions, may sensitize or otherwise damage liver cells in such a way as to produce acute yellow atrophy.

The author has been particularly interested in the possibility of increased toxicity when cinchophen is given in conjunction with iodin or iodids. We have attempted so far as records are available to determine what percentage of cases of toxicity due to cinchophen had taken iodids or iodin with the drug. The accompanying table, kindly prepared for me by a colleague, sets forth some of the facts in this connection. From this table it appears that 14 patients of the reported toxic cases had iodids administered with the cinchophen derivative. Of this number 6 died and the remaining 8 recovered. Five patients under observation at the present time are taking neocinchophen and potassium iodid. Four of these have had no digestive upsets, but one of them discontinued the iodid because of anorexia.

A patient recently seen at the Rockefeller Hospital, however, had been taking cinchophen for 1 week. She had been taking about 12 grains of cinchophen a day. She discontinued the cinchophen and took 5 drops of a potassium iodid solution 3 times a day for 3 or 4 days. Because of recurrence of pain she stopped the iodid and again took atophan, 8 grains a day for 8 days. Following

this period she again took potassium iodid. Seven days after taking the last dose of atophan she developed urticaria. The iodid was stopped. Three weeks later she became jaundiced. The patient recovered. It was thought that the poisoning was due perhaps to the combination of cinchophen and iodid. It is interesting that the patient, several years previous to this, had had an urticaria due to some food poisoning.

We have studied the records of 200 of our own patients who have taken either neocinchophen (tolysin) or cinchophen (atophan). (See Tables 1 and 2.) The patients have not been selected, but

TABLE 1.—TOLYSIN CHART.

Diagnosis.	No. of cases.	Previous gastrointestinal history.	Gastrointestinal effect.
Osteoarthritis	68	None	Indigestion, 2; nausea, 2; pain in stomach, 1; fainting spells, 1; dizzy, 1.
Infectious arthritis	104	Dig. upsets, 1	Nausea, 7; indigestion 5; burning in stomach, 1; rash, 3; nervousness, 2; vomiting, 1; palpitation, 1.
Neuritis	11	None	Fever, 1; nausea, 1; urticaria, 1.
Rheumatic fever	3	None	None.
Gout	1	None	None.

TABLE 2.—ATOPHAN CHART.

Diagnosis.	No. of cases.	Gastrointestinal effect.
Infectious arthritis	8	None
Osteoarthritis	6	Vomiting, 1*

* Patient who vomited after atophan had a previous history of loss of weight and appetite before taking the drug.

were consecutive admissions who had been given one of the cinchophen preparations. Most of the patients had been seen by the author. The material has been collected from private practice, St. Luke's arthritic clinic, and Post-Graduate Hospital arthritic clinic. In this series of 200, we have observed no instances of jaundice and there have been no fatalities. Fourteen had cinchophen (atophan) while 186 had neocinchophen (tolysin). Two patients had taken both cinchophen and neocinchophen. The dose varied from 15 grains in 1 day to 16,080 grains in 96 weeks. The drug in most instances was given in from 5- to 10-grain doses 3 times a day for 5 days a week. The patients in the majority of cases were also taking 3 gm. of sodium bicarbonate and the juice of a half lemon in a glass of water each day. In addition to tolysin or cinchophen, the patients were having other forms of treatment such as physiotherapy and vaccine therapy. All the patients with chronic infectious arthritis were receiving vaccine. In the appended table is recorded any history of previous gastrointestinal upsets or liver disturbances. There have been listed any digestive upsets that followed the ingestion of the drug. Of 200 patients, 22 complained of some digestive trouble. Only 2

of these vomited. One had taken 107 tablets of tolysin in 90 days while the other had taken 9 tablets of atophan. On 4 patients, not included in this series, we have determined the bile index before and after the ingestion of 150 grains of atophan. The icteric index was not found to be increased in any of these 4. Five patients developed a rash, 1 patient complained of palpitation and restlessness after he had taken 3 tablets. One fainted after she had taken 84 tablets in 2 weeks. Another developed a temperature after ingestion of 144 tablets in 4 weeks and 1 complained of extreme nervousness after he had taken 150 tablets in 25 days. One lady, aged 51 years, complained of dizzy spells after she had taken 120 tablets in 4 weeks. She stated that her pain completely disappeared with the use of tolysin, but that it made her so dizzy that she was unable to take it. However, since then she has been able to take 1 tablet a day without any difficulty. In all, 30 patients have manifested some toxic symptoms. None of these was of a serious nature, and none of the patients was confined to bed because of his symptoms. In the cases where vomiting, nausea or a rash appeared, the drug was discontinued. If the patient complained of indigestion to a very slight degree or beginning loss of appetite, he was given bicarbonate of soda in addition to the neocinchophen. If this were not satisfactory the cinchophen or neocinchophen was discontinued.

Four of the cases reported above are of such interest that they deserve more careful description.

Case Abstracts. Case 156. A nurse, aged 28 years, developed arthritis following the birth of her child 3 years previous. About a year before she was seen in the clinic, she had taken 1200 grains of cinchophen over a period of 1 month, an average of about 40 grains a day. At the end of this time nausea developed without vomiting. She then changed to neocinchophen and during the following 2 months took 1800 grains of that drug. After this urticaria appeared. She discontinued the drug for 4 weeks and then took 10 grains of neocinchophen and developed a severe urticaria. A month later, on request, she took 1 5-grain tablet of neocinchophen and immediately developed urticaria. One week later she took 6 tablets of the same drug and developed a rash. Her urine was tested at the time to determine the optical rotation and we were unable to find any trace of cinchophen in her urine. This test and its significance will be given more in detail later in the paper.

Case 149, aged 36 years, whose diagnosis was gout, after taking 5 grains of cinchophen became quite restless and after taking 15 grains became so nervous and his pulse became so rapid that he was given 8 minims of adrenalin. The drug was discontinued.

Case 150, aged 38 years, who was suffering from neuritis, gave a history of sensitiveness to aspirin and all salicylic acid preparations. Five grains of aspirin would produce severe urticaria. When first tried with tolysin she took it without any ill effect. This relieved her pain and she was most grateful, but after ingestion of 48 tablets over a period of 2 weeks, she developed severe urticaria and the drug had to be discontinued.

Case 148, aged 37 years, whose diagnosis was acute rheumatic fever, gave no history of digestive upsets until the onset of her present illness, at which time she vomited and developed an erythema. She was given

TABLE 3.—TABULATION OF CINCHOPHEN TOXICITY CASES.

Reference number.	Interval between first and second dose.	Iodin used.	Result.
Worster-Drought: Brit. Med. J. 1923, **1**, 148.	Present, 21 dys.	No	Recovery
Barron: J. Am. Med. Assn., 1924, **82**, 2010	Present, 3 yrs.	No	Recovery
Schultz: Deutsch. med. Wchnschr., 1929, **55**, 1972	Present, 3 mos.	No	Recovery
Cabot: Boston Med. and Surg. J., 1925, **192**, 1122	Unauthentic case	Unknown	Death
Petty: Brit. Med. J., 1928, **2**, 442	None	Unknown	Recovery
Löwenthal: Brit. Med. J., 1928, **592**, 1	None	No	Death
Klinkert: Therap. d. Gegenw., 1925. **67**, 334	None	No	Recovery
Klinkert: Ibid., 1926, **67**, 334	None	No	Recovery
Löwenthal: Brit. Med. J., 1928, **1**, 592	5 weeks	No	Death
Langdon-Brown: Brit. Med. J., 1926, **2**, 37	None	No	Death
Langdon-Brown: Ibid.	None	No	Death
Evans: Brit. Med. J., 1926, **2**, 93	None	No	Recovery
Evans: Ibid.	None	No	Recovery
Evans: Ibid.	None	No	Recovery
Glover: Brit. Med. J., 1926, **2**, 136	None	No	Recovery
Willcox: Brit. Med. J., 1926, **2**, 273	None	No	Death
Willcox: Ibid.	None	No	Recovery
Willcox: Ibid.	None	No	Recovery
Wells: Ibid., p. 759	None	No	Death
Klinker: Klin. Wchnschr., 1927, **6**, 24	10 days	No	Recovery
Kingreen: Deutsch. med. Wchnschr., 1927, **53**, 971	None	Yes	Recovery
Hitzenberger: Wien. klin. Wchnschr., 1927, **40**, 205	None	Yes	Death
Hitzenberger: Ibid.	None	Yes	Recovery
Schwartz: Wien. klin. Wchnschr., 1927, **40**, 238	None	Yes	Recovery
Singer: Ibid.	None	Yes	Death
Haudek: Ibid., 1929, **40**, 239	None	Yes	Recovery
Rake: Guy's Hosp. Rep., 1927, **77**, 229	None	No	Death
De Rezende. Brazil Méd., 1927, **41**, 1005	Doubtful	No	Recovery
De Rezende: Ibid.	None(?)	No	Recovery
De Rezende: Ibid.	None	No	Recovery
Rabinowitz: Med. Clin. N. A., 1928, **11**, 1025	None	No	Recovery
Weil: Med. Welt, 1928, **2**, 257	None	No	Death
Klinkert: Therap. d. Gegenw., 1928, **69**, 140.	None	No	Recovery
London Corresp., J. Am. Med. Assn., 1928, **90**, 1229	Unknown	Unknown	Death
Klinkert: Klin. Wchnschr., 1927, **6**, 24	None	No	Death
Dassen: Semana méd., 1929, **36**, 368	None	No	Recovery
Motzfeldt: Norsk Mag. f. Laegev., vol. **90**, p. 283	2 mos.	No	Recovery
Braun: J. Med. Assn. So. Africa, 1929, **3**, 157	None	Yes	Recovery
McVicar: Med. Clin. N. A., 1929, **12**, 1526	Short	No	Death
Frenzl: Wis. Med. J., 1929, **28**, 264	None	No	Recovery
Anderson: J. Am. Med. Assn., 1929, **93**, 93	6 weeks	Yes	Death
Reichle: Arch. Int. Med., 1929, **2**, 281	7 months	Yes	Death
Reichle: Ibid.	None	No	Death
Stacy and Van Zant: Minn. Med., 1930, **13**, 327.	Varying	No	Death
Schroeder: Ugesk. f. Laeger, 1922, **84**, 1141	14 days	No	Recovery
Schroeder: Ibid.	None	No	Recovery
Schroeder: Ibid.	Unknown	Unknown	Recovery
Schroeder: Ibid.	8 months	No	Death
Schroeder: Ibid.	None	No	Recovery
Schroeder: Ibid.	None	No	Recovery
Schroeder: Ibid.	None	No	Recovery
Schroeder: Ibid.	None	No	Recovery
Schroeder: Ibid.	None	No	Recovery
Schroeder: Ibid.	None	No	Recovery
Rabinowitz: J. Am. Med. Assn., 1930, **95**, 1228	None	Yes	Recovery
Rabinowitz: Ibid.	None	No	Recovery
Rabinowitz: Ibid.	None	No	Death
Rabinowitz: Ibid.	None	Yes	Death
Rabinowitz: Ibid.	None (Weldona case)	No	Recovery
Rabinowitz: Ibid.	(?)	No	Death
Sutton: J. Am. Med. Assn., 1925, **91**, 310	(?)	No	Death
Walker: New Eng. J. Med., 1931, **204**, 253	5 weeks	No	Death
Walker: Ibid.	6 months	No	Death
Parsons and Harding: AM. J. MED. SCI., 1931, **181**, 115	None	Possibility	Death
Parsons and Harding: Ibid.	None	No	Death
Parsons and Harding: Ibid.	None	No	Death
Parsons and Harding: Ibid.	None	No	Death
Beaver and Robertson: Proc. Mayo Clin., 1931, **6**, 261	Doubtful	No	Death
Beaver and Robertson: Ibid.	Doubtful	No	Death
Beaver and Robertson: Ibid.	Doubtful	No	Death
Beaver and Robertson: Ibid.	Doubtful	No	Death
Miller: J. Am. Med. Assn., 1931, **96**, 772	One year	Yes	Recovery
Cabot: Case Reports: New Eng. Med. J., 1931, **205**, 153	Doubtful	Yes	Death
Sherwood and Sherwood: Arch. Int. Med., 1931, **48**, 82	Doubtful	Yes	Recovery
Ross: Canad. Med. Assn. J., 1931, **24**, 632	(?)	No	Death
Ross: Ibid.	No interval	No	Death
Ross: Ibid.	(?)	No	Death
Ross: Ibid.	(?)	No	Recovery
Ross: Ibid.	None	No	Recovery

505 grains of neocinchophen without any untoward symptoms except a headache after the ingestion of 90 grains in 2 days. She was receiving 45 grains a day. She felt so well at this time that the drug was discontinued. Five days later she felt ill and again took the drug. After taking 30 grains her temperature rose to 99° F. and a rash developed. Adrenalin was given to control this. The drug was discontinued. Eleven days later 15 grains of aspirin were given and she again developed a rash.

Three of these 4 cases are reported in more detail because they lend evidence to the idea that it is possible for a patient to develop a sensitiveness to a drug which at first does them no harm. It is strange that one could take 3000 grains of cinchophen and neocinchophen without any untoward symptoms and then discontinue the drug and at some future time, even though it be a year or more distant, 5 grains of the drug would upset them. One should be doubly cautious in again administering the drug. It is most important to give a small initial dose to determine sensitivity. In reading the literature of the cinchophen poisoning cases, one is struck with the number of cases whose toxic symptoms have begun after the drug has been discontinued and then recommenced.

An attempt has been made to review the literature and determine how many of the fatal cases had taken the drug intermittently and what percentage of the toxic symptoms had occurred after the second and third courses of one of the phenylcinchoninic acid preparations. Fourteen of the 86 cases reported had an interval between their first and toxic doses. Five of these died. The results are given in Table 3.

Although no instance of acute yellow atrophy was observed in the 200 consecutive cases which were studied, yet an analysis of case histories at St. Luke's Hospital showed 2 instances of acute yellow atrophy in patients who had been taking either cinchophen or neocinchophen. Both of these patients had chronic infectious arthritis.

Case N. S., a woman, aged 45 years, had been given atophan and neocinchophen in large doses over a period of a year or more. The exact dose cannot be determined. She entered the hospital and died on the second day. The diagnosis was acute yellow atrophy; no causative agent other than the atophan could be found. Her urine was negative for arsenic. No autopsy was obtained.

Case B. K., a girl, aged 17 years, came to our office on November 5, 1928, and complained of arthritis of 4 years' duration. Two years prior to her visit she had had jaundice for 1 month. This was thought to be a catarrhal jaundice. She had been treated during the past 2 years at various hospitals. We have no record of the drugs which she had taken previously. She, however, stated that she had had milk and iron injections in one hospital and in another had had injections of protein which gave her chills. On November 14, 1928, she was admitted to St. Luke's Hospital to have a complete bacteriologic examination made of any foci of infections. An autogenous vaccine was prepared. On December 11 she returned to our office. Her temperature was 100° F. and she was having very severe joint pains. She was told to take 10 grains of tolysin 4 times a day. On December 18 she was given 0.03 cc. of autogenous vaccine. On December 22 she was

given 0.05 cc. of vaccine. On December 31 the patient developed a mild jaundice. She was admitted to St. Luke's Hospital on that day and a diagnosis of acute catarrhal jaundice was made. Her bile index was 186. On January 6 she became delirious and her temperature rapidly rose to 106° F. On January 7 she died, and a diagnosis of acute yellow atrophy was made. No autopsy was obtained.

It would be difficult to report this case as one of acute yellow atrophy proven to be due to tolysin because we had no autopsy, and furthermore we are not certain of the drugs she had taken before she came to us. Moreover, the patient had various protein injections and a history of jaundice, both of which are now known to be contraindications to the use of cinchophen preparations. It seems most likely, however, that this was a case of acute yellow atrophy and that the final exciting agent was tolysin. She received about 700 grains of tolysin over a period of approximately 3 weeks. This is only the second case that we have been able to find that might possibly be due to neocinchophen, and even in this case we have no absolute proof of the diagnosis.

Within the past year various investigators have sought independently to shed some light upon this toxicity question by laboratory methods. Among others we refer to Lichtman, quoted above, Churchill and von Wagoner,[45] Minot and Cutler, and my associate, Dr. A. J. Quick at Cornell University Medical School. Churchill and von Wagoner fed cinchophen to dogs in doses 27 times the calculated therapeutic dose (595 mg./K) mixed with their food. The urea nitrogen showed a marked rise, and at autopsy most of the dogs showed from one to three acute gastric ulcers and a number of yellowish areas over the surface of the liver, which on microscopic examination showed varying degrees of necrosis. Minot and Cutler[46, 47] have experimented with the idea that acute yellow atrophy is indicated by a high blood guanidin and a low blood dextrose. They believe that calcium gluconate tends to prevent acute yellow atrophy in dogs and in human beings.

Dr. A. J. Quick has very kindly done some analyses on urines of both patients and dogs. Five patients were examined, 2 of whom took cinchophen and 3 of whom took neocinchophen. The urines of the patients receiving cinchophen showed under polariscopic study a negative rotation directly proportional to the output of cinchophen. The neocinchophen urines, although the patients had received 30 grains a day for 7 days prior to collection of the specimen, produced no rotation of the plane of polarized light.

The author was one of the two who took the cinchophen. Urine was collected for 1 hour previous to the ingestion of 2 gm. of cinchophen. Blood uric acid was determined at this time on a fasting stomach. The uric acid was found to be 5.1 mg. per 100 cc. The volume of urine collected was 70 cc. The negative rotation was 0.15. One hour after the ingestion the volume of urine was 55 cc. and the negative rotation was 0.2. The blood uric acid was found

to be 4.3 mg. per 100 cc. Two hours after the ingestion of the cinchophen the volume of urine was 40 cc. and the negative rotation was 0.2. Three to 6 hours later the volume of urine passed was 140 cc. and the rotation was 0.35. The remainder of the 12-hour specimen which was collected showed a rotation of 0.2. From this observation it can be concluded that little if any of the cinchophen is excreted until 3 hours after its ingestion and that most of it is excreted 3 to 6 hours after the ingestion of the drug.

Experimental. Four dogs have been studied. The first dog weighed 8.4 kilos. She was given daily 5 gm. of cinchophen mixed with food scraps. Her appetite remained normal until the fifth day when she refused food and began to have severe diarrhea. She became very emaciated and would probably have died, if left unattended. For several days the dog was given nourishment by stomach tube and forced feeding; on the fourth day she again ate. Twelve days after the first dose of cinchophen was given the dog was normal, but still emaciated. At that time the dog was given sodium benzoate, which was conjugated normally. This we took to indicate that the liver was normal. Her urine had, throughout the experiment, marked levorotation. The second dog weighed 14.9 kg. She was fed a diet of casein, lard and sucrose and 5 gm. of cinchophen at 10 A.M. Eighty cubic centimeters of urine were collected from 10 A.M. to 4 P.M. The rotation was 1.10. From 4 P.M. to 10 P.M. 60 cc. of urine were collected. This had a negative rotation of 1.50; from 10 P.M. to 10 A.M. the next morning 93 cc. of urine were collected and the rotation was 2.00. The urine was first clarified with activated charcoal. The nature of the optically* active compound has not as yet been determined. It was first thought that the cinchophen was conjugated with glycuronic acid and that this conjugated substance was presenting the negative rotation. The third dog was given 2½ gm. of cinchophen by stomach tube. Three hours later the dog vomited. Three days later he was again given 2½ gm. by stomach tube. He developed marked tremor and seemed completely prostrated. He made complete apparent recovery in 6 hours. The next day he had no appetite. His icteric index was normal. The urine showed marked levorotation. The fourth dog was given 5 gm. of neocinchophen. This did not affect him in any way nor did his urine produce levorotation.

While the work of Lichtman has to a certain extent clarified the question of the excretion products of cinchophen, Dr. Quick and the author will attempt to pursue this study further in a laboratory way and report at a later date upon the products of cinchophen decomposition and the possibility of their conjugation with glycin.

Summary. 1. A study of 200 cases taking neocinchophen or cinchophen has been made. No fatal results were observed in these 200 cases, but 30 had some slight digestive or circulatory upsets. None was jaundiced.

2. A preliminary study on the excretion of cinchophen and neocinchophen preparations in human beings and dogs yielded the definite result that cinchophen develops a levorotary activity in the urine. In human beings most of the cinchophen is excreted within 3 to 6 hours after ingestion. In the urine of animals taking neocinchophen no such substance has been found.

* Optical rotation is expressed in degrees in 1-dm. tube.

3. The superiority of neocinchophen to cinchophen for general clinical use appears at the present time a fair conclusion from the evidence of the literature and the author's cases.

NOTE.—The writer wishes to acknowledge his indebtedness to Dr. R. H. Boots for his many helpful suggestions, to Dr. A. J. Quick for his laboratory studies and aid in the preparation of the laboratory portion of this paper, and to Dr. D. A. Bryce, Medical Director of the Calco Chemical Company, for his aid in the preparation of bibliography and tabulations upon the subject of phenylcinchoninic toxicity.

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REVIEWS.

A HANDBOOK OF OCULAR THERAPEUTICS. By SANFORD R. GIFFORD, M.A., M.D., F.A.C.S., Professor of Ophthalmology, Northwestern University Medical School, Chicago, etc. Pp. 272; 36 illustrations. Philadelphia: Lea & Febiger, 1932. Price, $3.25.

THE author has prepared a concise résumé of the nonsurgical methods of treatment used in ophthalmology. The first five chapters deal with the equipment advisable for routine ophthalmic practice, the commoner drugs and organ extracts used in ophthalmology, the value of specific and nonspecific protein therapy, and certain forms of physical therapy such as light, diathermy, the thermophore, Roentgen ray and radium. The action of the various drugs is described whenever this is known but many remedies are advised empirically with the frank statement that as yet we have no knowledge of their pharmacodynamics.

Practical application is made wherever possible of modern chemistry, for example, the authors advises making up various drugs in buffered solutions. The following solution is recommended for pilocarpin, zinc salts, cocain and adrenalin:

Boracic acid	6.2 gm.
KCl	7.4 gm.
H_2O	1000 cc.

This is an acid buffer solution with a pH of 5.5. A similar solution is recommended as a solvent for holocain with the addition of a few drops of dilute acetic acid. The following solution is recommended as a vehicle for atropin, homatropin, eserin and scopolamin:

Sodium bicarbonate	21.2 gm.
H_2O	1000 cc.

This is a slightly alkaline buffer solution with a pH of 7.6. A third medium which acts as a neutral buffer is a 3 per cent solution of gelatin in a solution of water. This is recommended as a vehicle for antiseptics, since they are less irritating in this form than in aqueous solutions and the gelatin spreads in a thin film over the conjunctiva and remains in contact with it longer than aqueous solutions. The author gives his routine method for the administration of tuberculin therapeutically.

The last 11 chapters deal with the treatment of diseases of the eye arranged in anatomic order, as diseases of the lids, conjunctiva, cornea, uveal tract, etc. The author's point of view recommending a new procedure is best exemplified by the following paragraph in the introduction:

"A position of therapeutic nihilism, or of unreasoning scepticism with regard to new agents and methods, is equally fallacious, as in the position of resting content with time-honored methods, some of which have nothing but the sanction of years to justify their continued use."

F. A.

LES MALADIES DE L'ESPRIT ET LEURS MÉDECINS DU XVI^e AU XIX^e SIÈCLE. By M. LAIGNEL-LAVASTINE and JEAN VINCHON. Pp. 377; illustrated. Paris: Norbert Maloine, 1930.

THIS handsome volume aims to delineate the principal stages in the evolution of psychiatry in the last four centuries. Realizing that this specialty may be studied not only in the bodies of patients but also in their writings, paintings or in fact in any objective creation of their diseased minds, the authors rightly emphasize the practical clinical value of the historic method, as well as its cultural edification. Their plan of procedure is to present some 24 essays, arranged according to the chronology of the subject matter and joined together by the guiding motif already mentioned. Thus in the 16th century chapters von Schenck, von Grafenberg and Paré present their neuropsychiatric concepts, to be followed by essays on the genesis of modern ideas of the insane, incubi, etc. In the 17th century, Willis, Ettmuller, Diemerbroeck and Zacchias are covered; while in the 18th, de la Metterie, the encyclopedists, Hecquet, animal magnetism and the precursors of Boyle furnish the subject matter. Pinel is taken as the representative of the 19th century and the volume concludes with an essay on the evolution of the treatment of the psychoses. E. K.

HISTORY OF MEDICINE IN THE UNITED STATES. By FRANCIS R. PACKARD, M.D., Editor, Annals of Medical History. 2 vols. Pp. 1323; 103 illustrations. New York: Paul B. Hoeber, Inc., 1931. Price, $12.00.

IT is now 30 years since the first edition of this work appeared; for many of these years it has been out of print, yet it is still the only book covering the subject as a whole. The new edition has, therefore, been awaited with interest for some time and it now appears considerably enlarged and in a new format of two stately volumes of Hoeber's well-known dark blue. Nevertheless, "no attempt has been made to consider the wonderful things accomplished by the great foundations for research, medical education and hygiene which have come into being in the United States in late years, their origin being too recent to permit of their being included in a work which purports to be truly historical"; neither has it seemed advisable to the author to change to any extent the method of approach of the former edition which is partly chronological and partly by special topic. Thus in the first volume after a chapter on colonial medicine, the other 8 chapters treat of epidemics in the English colonies up to 1800, medical legislation, the earliest hospitals, pre-scholastic medical education, the earliest schools, pre-Revolutionary publications, Revolutionary medicine and Army medicine to the close of the Spanish War (this last written by Colonel Ashburn thus unfortunately not including the splendid story of the conquest of yellow fever). The second volume opens with a chapter by Lieut. Commander Parsons on the medical department of the U. S. Navy, followed by others on some of the medical schools founded during the first half of the nineteenth century, outlines of the development of medical practice and education in some of the states, foreign influences on American medicine, some notable events in American medicine and surgery, and the beginnings of specialism in America. A series of 11 useful Appendices, mostly on eighteenth century matters, also includes useful information on the Ether Controversy, Women in Medicine and notes on regular and irregular Medical Schools in the United States. A bibliography of 24 pages and 2 good indexes complete the value of the work.

Regard for the personality of the author, his individual historical contributions and the great service he is rendering to medical history through

the Annals of Medical History, all make it difficult to appraise this work objectively. However, all must concede that it was and now, still more, is the most important existing book on the history of American medicine. The author has apparently not intended it to be in any sense a complete record of events either in form or quantity and in the Preface himself points out its unevenness and its omissions. While we can only regret that a person so eminently fitted for the job has not been permitted by the rigors of "chasing that damned guinea" to produce an adequate history in the conventional sense, we can be thankful for this series of vivid narrations and evaluations, covering so many phases of American medicine in such an interesting way. Let us hope that before another 30 years have passed, a well-earned repose will permit the author to add to his material and rearrange it into a standard history that will take rank with such great American works as Garrison's History, Cushing's Life of Osler and Sarton's Introduction to the History of Science. E. K.

ROENTGENOLOGIC STUDIES OF EGYPTIAN AND PERUVIAN MUMMIES. Anthropology Memoirs. Vol. III. By ROY L. MOODIE, Paleopathologist to the Wellcome Historical Museum, London. Pp. 62; 76 plates in photogravure, chiefly from roentgenograms. Chicago: Field Museum of Natural History, 1931. Price, $5.00.

THE author's widely known works on paleopathology are well supplemented by this roentgenologic study of Egyptian and Peruvian mummies made in the Division of Roentgenology of the Field Museum. In spite of occasional obscuration caused by dense embalming materials or objects included in the coffin, or by other technical difficulties, the beautifully made and beautifully reproduced pictures show a considerable number and variety of diseases. The author estimates that "among the pre-Columbian Peruvian mummies the incidence of disease and injury is 10.52 per cent," with 40 per cent among the Egyptians; though his numbers are really much too small for statistic solidity. Although the body of the text is chiefly occupied by detailed descriptions of the 53 mummy packs studied, there are interesting summaries of the Development of Roentgenologic Study of Mummies, Peruvian Mummification, Pre-Columbian Pediatrics and similar topics. The Field Museum is to be congratulated on this valuable production with its splendid reproductions. E. K.

THE ETHNO-BOTANY OF THE MAYA. Publication No. 2 of the Tulane University of Lousiana, Middle American Research Series. By RALPH L. ROYS. Pp. 359. New Orleans: The Department of Middle American Research, The Tulane University of Lousiana, 1931.

WE have elsewhere made the statement that medical aspects of the Mayan civilization constitute an appropriate and probably a fruitful field for the new school of medical historians in this country to pursue. From this point of view the present volume assumes new importance. Coming at a time when the Mayan culture is being actively explored in various ways, it gives a scholarly presentation of a field that, except for the work of the Heye Foundation and the Peabody Museum, has had but little attention from American schools. The survey of Mayan materia medica is classified under some two score groups of diseases such as Poisoning, Ear Complaints, Skin Diseases, Ulcers, Abscesses, Cancer and Tumors (the largest section), etc. In each case the Mayan prescription is first given (a key to pronuncia-

tion being provided), and the English translation following. A list of Mayan fanna names and an extensive bibliography add to the usefulness of the book. We congratulate Tulane on this praiseworthy production.

The following publications have already been published or are about to appear in this series: Tribes and Temples, by Frans Blom and Oliver LaFarge, II; the Year-Bearer's People, by Oliver LaFarge, II, and Douglas Byers; Miscellaneous Papers Pertaining to Research in Middle America, written by friends and the staff of the Department of Middle American Research of Tulane University; Herman Beyer on Maya Hieroglyphs; Frans Blom on the Ruins of Uxmal, Yucatan; Miscellaneous Linguistic Manuscripts in the Library of the Department of Middle American Research of Tulane University. E. K.

THE FACTOR OF INFECTION IN THE RHEUMATIC STATE. By ALVIN F. COBURN, Resident Physician, Presbyterian Hospital, New York City. Pp. 288; 48 illustrations. Baltimore: The Williams & Wilkins Company, 1931. Price, $6.00.

A CONCISE, thorough, scientific study of the rôle of infection in the rheumatic state. The material is ably presented, in a well illustrated and printed book. An important contribution to the subject. G. W.

CLINICAL OBSERVATIONS ON THE SURGICAL PATHOLOGY OF BONE. By DAVID M. GREIG, M.B., C.M., F.R.C.S. (EDIN.), F.R.S.E., Conservator of the Museum of the Royal College of Surgeons of Edinburgh. Pp. 248; 224 illustrations. Edinburgh: Oliver & Boyd, 1931. Price, 30/- net.

IN this beautifully illustrated monograph are presented the opinions of a clinical surgeon upon the more common bone lesions. An attempt is made to condense and correlate a number of the formerly uncorrelated pathologic processes of bone disease.

The works of Leriche and Policard have strongly influenced the opinions of the author, many of whose views are unorthodox.

The monograph is interesting and well worth serious study. An easily following style facilitates the reading of the treatise. G. W.

CONTROL OF CONCEPTION. By ROBERT LATOU DICKINSON and LOUISE STEVENS BRYANT. Pp. 290; 72 illustrations. Baltimore: The Williams & Wilkins Company, 1931. Price, $4.50.

THE book is a most careful and detailed compilation of all that is at present known upon the subject of the control of conception. Each phase of this many-sided problem is reviewed and scrutinized in a most scholarly and impartial fashion. The collective experience of many sources of information is set forth in due order and with painstaking care. The whole text is liberally illustrated with exceedingly clear illustrations, of a semidiagrammatic nature, all accurately drawn to scale.

The subject matter is presented in nine chapters which are as follows: An introduction; a detailed and careful review of the anatomy and physiology of the generative organs of both sexes; the technique of contraception—a long chapter in which all known methods are presented and evaluated; the next three chapters, on sterilization without unsexing, early

therapeutic abortion, sterilization and contraception, are brief and lucid; the final three chapters, on clinic organization and service, the legal status of contraception and sterilization, and the general philosophy of contraceptive methods, are an admirable charting of the facts, actually learned by experiences in this rather nebulous and neglected branch of science. The keynote of the book is sounded in the final chapter, in which the authors stress the incompleteness of our knowledge and pleads for further organized coöperation from many agencies to complete our information. O. T.

TUMORS OF BONE. By CHARLES F. GESCHICKTER, M.D., Surgical Pathologic Laboratory, Department of Surgery, Johns Hopkins Hospital and University, Baltimore, and MURRAY M. COPELAND, M.D., Memorial Hospital, New York City. With Forewords by DEAN LEWIS, M.D., and JOSEPH COLT BLOODGOOD, M.D. Pp. 709; 406 illustrations. New York: The American Journal of Cancer, 1931. Price, $5.00.

HERE is a monumental and pioneer work on bone tumors. The work is of importance chiefly because of the critical analysis of the subject and the excellent condensation and correlation of the material. Much of the book has appeared during the past year and a half in the Archives of Surgery.
G. W.

THE FUNDUS OF THE HUMAN EYE. By ERNEST CLARKE, C.V.O., M.D., F.R.C.S., Consulting Surgeon to the Central London Ophthalmic Hospital, etc. Preface and Table of Contents, with 51 colored plates. New York: Oxford University Press, 1931.

THIS book is composed of a series of 51 illustrations of the fundus oculi by the Editor of the *Haab's Atlas of Ophthalmoscopy*. The illustrations are taken from a collection of paintings owned by Hamblin Company and are generally very good. The descriptions of the plates are too scant.
F. A.

IMHOTEP TO HARVEY. BACKGROUNDS OF MEDICAL HISTORY. By C. N. B. CAMAC, M.D., Assistant Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University. Foreword by HENRY FAIRFIELD OSBORN, Sc.D., LL.D. Pp. 324; 2 figures. New York: Paul B. Hoeber, Inc., 1931. Price, $3.75.

THE present volume, as its subtitle implies, may well be used as an introduction to the subject of medical history, which later perhaps may be read in greater detail piecemeal or in larger works. The basis of the author's well-known Seminars in the library of the College of Physicians, it aims at and succeeds in presenting a comprehensive outline, of which the body or any part of it can be filled in by the individual *ad lib*. Thus biographic details are conspicuous by their absence. Imhotep, for instance, appears on the tital page and list of books only, while both the historical settings of the different periods and the other sciences related to medicine are treated with corresponding liberality. This tends toward a closely woven argument, relatively unencumbered by too many obstructing details, and promotes continuous reading. Most of the 10 chapters are chronologic, though they are preceded by one on the Evolution of Inquiry

and followed by another on Schools of Thought in Medicine, while an especially interesting discussion of the Environment of the Inquirer in the Mediæval and Renaissance Periods follows these two chapters. The chronologic chapters are each preceded by a useful table, subdivided into "Pursuits," "Medical Practice Based On," "Records," "Writers and Teachers." Appendices of Historic Records (in continuation of an earlier work of the author's) and a List of Books are as welcome as the lack of an index is regretted. A curious printer's pie at the bottom of page 69 is one of the few slips in a book which in type, paper, proportions and binding continues the high standard of Hoeber's blue series. We believe that this will prove for most readers the most instructive and entertaining of any of the smaller books covering the whole field of the history of medicine.

E. K.

THE PRACTICE OF CONTRACEPTION. Edited by MARGARET SANGER and HANNAH M. STONE, M.D., with a Foreword by ROBERT L. DICKINSON, M.D. Pp. 300; 22 illustrations. Baltimore: The Williams & Wilkins Company, 1931. Price, $4.00.

THIS book is an international symposium and survey of the practice of contraception, the material being taken from the proceedings of the Eleventh International Birth Control Conference, held at Zürich, Switzerland, in September, 1930. The material which consists of papers on various phases of contraceptive practice, both practical and experimental, and the discussions these papers provoked, is divided into four main headings: The first deals entirely with actual methods of contraception practice—it takes 175 pages; the second deals with abortion only, and takes only 25 pages; the third gives detailed description of the operations of the existing birth control clinics in the various countries and their struggles in coming into existence; the fourth is a summary of the material already presented.

The book is of extreme interest to anyone already well informed on various phases of contraceptive practice. The views expressed by the various authors in the papers and discussions are of so conflicting a nature as to make the book unsuitable for a textbook or guide to a practitioner.

O. T.

MANUAL OF SURGERY. VOL. II. EXTREMITIES: HEAD AND NECK. By ALEXANDER MILES, M.D., LL.D., F.R.C.S. (EDIN.), Consulting Surgeon, Royal Infirmary, Edinburgh, and D. P. D. WILKIE, M.D., F.R.C.S. (EDIN. and ENG.), Professor of Surgery, University of Edinburgh. Pp. 685; 303 illustrations. Eighth edition. New York: Oxford University Press, 1931. Price, $3.80.

ABOUT one-half of the volume is given over to a discussion of fractures and orthopedic diseases. The discussion of fractures in general is improved over that found in the earlier editions but the methods suggested and the illustrations in many cases do not come up to the standard of American texts. Brief discussions of injuries and diseases of the skull and brain are followed by a description of the diseases of the spine and spinal cord. The final chapters of the book treat of the surgical conditions of the face, mouth, ears and neck. A rather complete chapter is given on the thyroid gland. The book has been brought up to date in many respects but many of the illustrations are poor and no attempt has been made to recommend some of the more recent operative methods.

L. F.

MANUAL OF SURGERY. VOL. III. THORAX AND ABDOMEN. By ALEXANDER MILES, M.D., LL.D., F.R.C.S. (EDIN.), Consulting Surgeon, Royal Infirmary, Edinburgh, and D. P. D. WILKIE, M.D., F.R.C.S. (EDIN. and ENG.), Professor of Surgery, University of Edinburgh. Pp. 578; 177 illustrations. Eighth edition. New York: Oxford University Press, 1931. Price, $3.80.

THE first part of the book treats of diseases of the chest, heart and breast. Then follows a more complete discussion of the diseases of the abdomen and pelvis. Peritonitis, appendicitis, hernia, diseases of the stomach, intestinal obstruction and diseases of the colon, rectum and anus are described in the order named. This portion of the book has been completely revised and numerous excellent illustrations have been added. The chapter on Diseases of the Liver and Bile Passages has been brought to date. A very short chapter on Intra-abdominal Gynecologic Conditions is followed by a long section on genitourinary diseases. The method by which each section is introduced is the same in all of these volumes. A brief discussion of the anatomy and physiology of the part is presented, followed by a section on the methods of investigation and of critical examination of the organ under consideration. Various clinical tests are outlined in this section and, finally, there is appended a list of definitions describing the names of the operations performed on the organ. This revision of the standard surgery of Thomson and Miles again modernizes this system of surgery. It does not attempt to describe any of the operative methods. It should be found useful, as it has been in the past, as a ready reference on the subject of surgical diseases.

L. F.

A SYSTEM OF BACTERIOLOGY IN RELATION TO MEDICINE. VOL. VIII. FUNGI, STREPTOTHRICEÆ, SPIROCHÆTES, NORMAL FLORA, SWINE ERYSIPELAS. By VARIOUS AUTHORS. Pp. 389; illustrated. London: Medical Research Council, 1931. Price, £1.1.9 for this volume; for the set, £8.14.9. Obtainable in the United States at British Library of Information, 5 E. 45th St., New York.

A REMARKABLY rich fund of information is contained in the 389 pages. The concise, pointed English style of previous volumes is continued in this one; the frank, critical attitude is welcome in view of the authority behind it. The chapters cover the following subjects: Fungi Pathogenic to Man; Actinomycosis and Similar Conditions; Pathogenic Leptothriceæ; The Spirochætes; Commensal Spirochætes; Blood Spirochætes; Syphilis; Ratbite Fever or Sodoku; The Leptospiroses; Yaws; The Normal Bacterial Flora of Man; Swine Erysipelas.

The chapter on Pathogenic Fungi has been long awaited by English-speaking peoples. It is valuable because the viewpoints both of the systematic botanist (Ramsbottom) and the clinical pathologist (Whitfield) are submitted.

The Reviewer notes a few typographic errors, as in the spelling of "dermatitidis" and of "tulanensis" on page 20. The distinction between actinobacillosis and actinomycosis properly receives emphasis, an entire section being devoted to actinobacillosis.

Syphilis is brought down to date, including discussion of involution forms of T. pallidum. Singularly, "spirocheta" is permitted in preference to "treponema" in a systematic treatise such as a System of Bacteriology; "it seems most convenient here to refer to it as 'S. pallida'" (page 187) is offered in extenuation.

The section on yaws includes the immunologic relationships with syphilis. A most welcome chapter is that on the normal bacterial flora of man. This

covers the skin, mouth, respiratory tract, vagina and the gastrointestinal tract.

The important section on spirochetes is the only one covered by illustrations; perhaps the lack of illustrations is the most serious criticism of the entire work, although a fuller index would help in many places. No doubt these shortcomings are enforced by a policy directed in favor of a compact volume.

The final chapter, on Swine Erysipelas, represents an abstract *in extenso* of much-scattered material in the literature.

The volume is a praiseworthy and most welcome addition to the armamentarium of English-speaking physicians—both laboratory and clinical; in fact, it is hard to see how the up-to-date laboratory man who is limited to the English language could fairly do without the subject matter it contains.

F. W.

THE STORY OF MEDICINE. By VICTOR ROBINSON, M.D., Professor of History of Medicine, Temple University School of Medicine, Philadelphia. Pp. 527. New York: Albert and Charles Boni, 1931. Price, $5.00.

THIS book is aptly named. Though covering the whole period of medicine in 12 conventionally divided chapters, it is rather an entertaining, chronologically arranged combination of stories and quotations than a detailed exposition like the more customary histories of medicine. The author's wide knowledge, his flair for the curious yet characteristic, and his ability to paint a vivid picture have combined to produce a work that welds a wealth of historical lore to an entertaining narrative such as may not be found in any other work in this field. "When a king is the librarian of his nation, the results are astonishing;" "the silent Sphinx of Giza gazes eastward over the Nile Valley and has no message for the younger nations;" "with such gibberish Cato the Censor kept Hippocrates at bay;" "their (the ancients) utter disregard for quotation marks has wrinkled the brow of posterity;" "the laughter of Molière was the savior of medicine in the seventeenth century" may serve as characteristic aphorisms to illustrate the piquancy of this interesting production. With so much to praise, it may appear as carping criticism to observe that "the vapor of ether that has spread like a benediction" first arose for anesthetic use, not from the Massachusetts General Hospital, but from a Georgia village, and that "the alien from Japan" unfortunately did not discover the germ of yellow fever in Ecuador. The author's free use of quotations promotes a desirable first-hand acquaintance with his heroes, while the frequent inclusion of border topics, such as astrology, scholasticism, university education, botany, Renaissance art, electricity, evolution and so on, tends to a breadth of treatment that adds both to the charm and value of this highly praiseworthy production.

E. K.

MANUAL FOR THE JEWISH DIABETIC. By WILLIAM S. COLLENS, B.S., M.D., Assistant Chief, Diabetic Clinic, United Israel Zion Hospital. Foreword by HENRY JOACHIM, M.D., Clinical Professor of Medicine, Long Island College of Medicine, Brooklyn. Pp. 138; 21 illustrations. New York: Bloch Publishing Company, 1931.

LIKE similar primers, this volume endeavors to give the patient a clear idea about diabetes. The author discusses the causes of diabetes, its complications, the method of urinalysis, the usual facts concerning the use of insulin, proper hygiene and the dietetic management. Food values, recipes and menus are given with special consideration for the Jewish diabetic. The description of the technique for testing the urine for sugar and that describing how to take insulin are unusually well done because each step is illustrated. The book is well written and comprehensive and is recommended for Jewish patients.

L. J.

BOOKS RECEIVED.

NEW BOOKS.

Fungous Diseases. By HARRY P. JACOBSON, M.D., Attending Dermatologist and Member of the Malignancy Board, Los Angeles County General Hospital. With Introductions by JAY FRANK SCHAMBERG, M.D., Professor of Dermatology and Syphilology, Graduate School of Medicine, University of Pennsylvania, and HOWARD MORROW, M.D., Clinical Professor of Dermatology, University of California Medical School. Pp. 317; 153 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, $5.50.

Nursing in Nervous Diseases. By JAMES MCCONNELL, M.D., Neurologist to the Philadelphia General Hospital; Associate Professor of Neurology, Graduate School of Medicine, University of Pennsylvania. Pp. 153; 24 illustrations. Philadelphia: F. A. Davis Company, 1932. Price, $1.50.

Introduction to Dermatology. By RICHARD L. SUTTON, M.D., Sc.D., LL.D., F.R.S. (EDIN.), Professor of Diseases of the Skin, University of Kansas School of Medicine, and RICHARD L. SUTTON, JR., A.M., M.D., Visiting Dermatologist to the Kansas City General Hospital. Pp. 565; 183 illustrations. St. Louis: The C. V. Mosby Company, 1932. Price, $5.00.

Classic Descriptions of Disease. By RALPH H. MAJOR, Professor of Medicine, University of Kansas School of Medicine. Pp. 630; 127 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, $4.50.

The Surgical Clinics of North America, Vol. 12, No. 4 (Mayo Clinic Number, August, 1932). Pp. 227; 79 illustrations. Philadelphia: W. B. Saunders Company, 1932.

The Sputum. By RANDALL CLIFFORD, M.D., Associate in Medicine, Peter Bent Brigham Hospital; Assistant in Medicine, Harvard Medical School. Pp. 167; 21 illustrations and 7 plates in color. New York: The Macmillan Company, 1932. Price, $4.00.

The Science of Signs and Symptoms. By ROBERT JOHN STEWART MCDOWALL, D.Sc., M.B., F.R.C.P. (EDIN.), Professor of Physiology, King's College, University of London, etc. Pp. 440; 6 illustrations. New York: D. Appleton & Co., 1932. Price, $7.00.

Clinical Endocrinology of the Female. By CHARLES MAYER, M.D., F.A.C.S., Assistant Professor of Gynecology and Obstetrics, Graduate School of Medicine, University of Pennsylvania, etc., and LEOPOLD GOLDSTEIN, M.D., Demonstrator of Obstetrics, Jefferson Medical College, etc. Pp. 519; 117 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, $6.00.

Clio Medica, Vol. III, Physical Therapy. By JOHN S. COULTER, M.D., Assistant Professor of Physical Therapy, Northwestern University Medical School, Chicago. Pp. 142; 15 illustrations. New York: Paul B. Hoeber, Inc., 1932. Price, $1.50.

Functional Disturbances of the Heart. By HARLOW BROOKS, Attending Physician, Fourth Medical Service, Bellevue Hospital, etc. Pp. 288. Philadelphia: J. B. Lippincott Company, 1932. Price, $5.00.

A Textbook of Pathology. By WILLIAM BOYD, M.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.), DIPL. PSYCH., F.R.S.C., Professor of Pathology, University of Manitoba; Pathologist to the Winnipeg General Hospital. Pp. 946; 287 engravings and 1 colored plate. Philadelphia: Lea & Febiger, 1932. Price, $10.00.

Orthopedics in Childhood. By WILLIAM L. SNEED, M.D., Attending Surgeon, Hospital for the Relief of the Ruptured and Crippled, etc. Every Day Practice Series, edited by HARLOW BROOKS, M.D. Pp. 318; 145 illustrations. Philadelphia: J. B. Lippincott Company, 1931. Price, $5.00.

Posture. By FRANK D. DICKSON, M.D., Orthopedic Surgeon, St. Luke's Hospital and the Kansas City General Hospital. Every Day Practice Series, edited by HARLOW BROOKS, M.D. Pp. 213; 118 illustrations. Philadelphia: J. B. Lippincott Company, 1931. Price, $5.00.

Functional Disorders of the Gastrointestinal Tract. By WILLIAM GERRY MORGAN, M.D., F.A.C.P., Professor of Gastroenterology, Georgetown University Medical School, etc. Every Day Practice Series, edited by HARLOW BROOKS, M.D. Pp. 259; 32 illustrations. Philadelphia: J. B. Lippincott Company, 1931. Price, $5.00.

Publications of the Committee on the Costs of Medical Care. No. 17. Nursing Services and Insurance for Medical Care in Brattleboro, Vt. By ALLON PEEBLES, PH.D., and VALERIA D. MCDERMOTT. With an Evaluation of the Nursing Program by VIOLET H. HODGSON, R.N., Assistant Director, and KATHARINE TUCKER, R.N., General Director, of the National Organization for Public Health Nursing. Pp. 65. *No. 18. The Medical Service of the Homestake Mining Company.* By LOUIS S. REED, PH.D. Pp. 54. Chicago: University of Chicago Press, 1932. Price, 60c each.

The Cardiac Output of Man in Health and Disease. By ARTHUR GROLLMAN, PH.D., M.D., Associate Professor of Physiology in the Medical School of the Johns Hopkins University. Pp. 325; 14 figures and 57 tables. Springfield, Ill.: Charles C Thomas, 1932. Price, $4.00.

The Advance of Medicine. By RT. HON. LORD MOYNIHAN, K.C.M.G., C.B., President, Royal College of Surgeons of England. Pp. 64. New York: Oxford University Press, 1932. Price, $1.00.

In Memoriam. Army Medical Bulletin No. 27. Supplement to Vol. I of the Medical Department of the United States Army in the World War. Pp. 37. Carlisle Barracks, Pa.: Medical Field Service School, 1932.

NEW EDITIONS.

A Descriptive Atlas of Radiographs. By A. P. BERTWISTLE, M.B., CH.B., F.R.C.S. (EDIN.). Pp. 552; 767 illustrations. Second edition revised and enlarged. St. Louis: The C. V. Mosby Company, 1932. Price, $13.50.

Minor Surgery. By FREDERICK CHRISTOPHER, S.B., M.D., F.A.C.S., Assistant Professor of Surgery at the Northwestern University Medical School, Chicago. With a Foreword by ALLEN B. KANAVEL, M.D., F.A.C.S., Professor of Surgery at the Northwestern University Medical School. Pp. 998; 687 illustrations. Second edition reset. Philadelphia: W. B. Saunders Company, 1932. Price, $10.00.

Essentials of Pediatric Nursing. By RUTH ALICE PERKINS, R.N., B.S., Graduate of Children's Memorial School of Nursing, Chicago, etc. Pp. 467; 55 engravings and 6 full-page colored plates. Second edition revised and enlarged. Philadelphia: F. A. Davis Company, 1932.

Handbook of the Vaccine Treatment of Chronic Rheumatic Diseases. By H. WARREN CROWE, D.M., B.CH. (OXON.), M.R.C.S., L.R.C.P., Director of the Charterhouse Rheumatism Clinic, etc. Pp. 79. Second edition. New York: Oxford University Press, 1932. Price, 80c.

L'Inspection Médicale des Écoles. By DOCTEUR MAURICE DUVERNOY, Professeur à l'École de Médecine de Besançon; Directeur de l'Institut d'Education Physique de Franche-Comté. Pp. 236. Second edition. Besançon: V. Chicandre, 1932.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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AND

JOHN H. MUSSER, M.D.,

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The Nature of Allergy in Tuberculosis as Revealed by Tissue Culture Studies.—It might be well to note some additional experimental evidences concerning the rôle of allergy in the production of adult tuberculosis, bearing in mind that there are many to whom this conception of tissue reaction in tuberculosis is not acceptable. In this present study (RICH and LEWIS, *Bull. Johns Hop. Hosp.*, 1932, **50**, 115) living cells from animals rendered allergic to old tuberculin were studied. These cells were washed and contrasted with cells from normal animals in plasma from the allergic as well as the normal, treated with a preparation of old tuberculin. Marked damage was done to the allergic cells by the tuberculoprotein. It is clear from these studies that the living cells from the allergic tuberculous animal, even when washed, retain their hypersensitivity to tuberculin when separated from the body by means of tissue culture. From direct findings "neither the circulatory, nervous nor other mechanisms dependent upon the intact body are necessary for the production of allergic damage." The antibody is attached intimately to the cell itself.

Insulin Therapy.—When insulin was first used in the treatment of diabetes frequently there occurred rather severe skin reactions. It soon became apparent that most of these reactions were due to chemical irritants contained in the pancreatic extracts. There was fear in the early days of insulin that there might occur severe allergic reactions, particularly in those individuals who already had insulin and then were obliged to discontinue it. This fear was not substantiated, however, and insulin therapy has been used extensively for nearly a decade now without record of any known fatality as a result of allergic reactions in sensitized individuals. However, reports of cases of insulin hypersensitiveness have appeared from time to time and undoubtedly local reactions occur in a considerable number of instances. Lawrence is

quoted as saying that such reactions occur in 20 per cent of his cases, whereas Joslin is recorded as stating that local reactions occur in about 10 to 20 per cent of his cases during the first weeks of treatment, although systemic reactions average 1 in 1000 diabetics. There is apparently an increasing number of individuals who have some local reaction to the injection of insulin. This statement is confirmed by an article written by ALLAN and SCHERER (*Endocrinology*, 1932, **16**, 417), who have made a statistical study of the incidence of insulin allergy in the Mayo Clinic and found that allergic reactions are on the increase. In 1927, for example, of 428 patients treated 14 showed such reaction, a percentage of 3.2, whereas in 1930 of 401 patients treated 56 had allergic reactions, a percentage of 13.8, and in the first 6 months of this year 14.1 per cent had reactions following the introduction of insulin. An explanation for the increase is not apparent. The possibility exists that because more people have had insulin, sensitization may have occurred because of this but there is an increased incidence of hypersensitiveness in patients who have never had insulin. There has been no apparent change in the quality of insulin but there appears to be a variability in behavior with different lots of the preparation. The authors detailed the type of reaction in their last 100 cases in which this happened. Eighty-four showed a mild allergic local reaction characterized by immediate stinging, burning pain at the site of injection followed an hour or two later by swelling of the tissues and redness of the skin, associated with burning and itching, and disappearing from 1 to 3 days. Twelve of the group had a somewhat more severe reaction as shown by intense inflammatory change in the injected skin and subcutaneous tissue, at times associated with fever and malaise, the local lesion not subsiding for at least a week. A general allergic reaction was seen in 4 cases manifested by subcutaneous, circulatory, and at times, gastrointestinal symptoms and in one instance a generalized dermatitis. The severe symptoms come on immediately but the signs of circulatory collapse subside within an hour or two. These severe general reactions occur only in patients who have had insulin and then have ceased. There is not very much question but that these reactions represent true hypersensitiveness to insulin, proven in part by cutaneous tests which were strongly positive. The importance of the skin test must be discounted to a certain extent in that positive reactions occur at times in individuals who show no hypersensitiveness. In these 100 patients desensitization was spontaneous in 8. There were 64 instances in which relief followed change in the type of insulin. In 22 instances in which nothing could be done to relieve the symptoms, fortunately it was possible to stop insulin after the diet had become satisfactorily adjusted but in 6 cases of severe diabetes nothing that was tried had any effect on the reaction of the patient. It was necessary to continue with the insulin. In none of these patients was there any interference by the hypersensitivity with the effect of insulin on the diabetes. Such cases have been reported, an example of which is quoted by the authors in which 600 to 700 units of insulin were required daily, and another instance in which apparently the injection of insulin interfered with the action of the insulin secreted by that particular individual's pancreas. The authors found no such cases in their series. They raise the question of how such cases should be treated and suggest

the following policy: Control the diabetes by diet if possible. If this cannot be done insulin must be employed as the danger from a diabetic death is greater than from an allergic death. Change the preparation. If there is still an allergic reaction attempt to desensitize by minimum dosage and increase gradually. Local measures such as soothing lotions are not much help nor is mixing the insulin with a local anesthetic, nor varying its reaction. Calcium has been of no value. In reviewing this interesting paper the thought arises as to the danger of administering insulin intravenously to those patients who come into general hospitals in coma who previously had insulin and discontinued it. This is an extremely common occurrence in large general charity hospitals and it is quite possible that insulin may have caused death in a certain number of instances as a result of anaphylactic reaction rather than death from diabetic coma. It might seem that a policy of caution should be followed in administering insulin intravenously to patients who have previously had this specific preparation and who have discontinued it, ultimately slipping into coma.

SURGERY

UNDER THE CHARGE OF
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The Colon as a Site of Focal Infection in Nonspecific Urethritis.—REDEVILLE (*Urol. and Cutan. Rev.*, 1931, **25**, 620) says that the experimentation has proved that bacteria from the colon can pass through its walls into the lymphatic and blood stream through the kidneys and produce a nonspecific urethritis. The verumontanum is like a weather gauge indicating various conditions in the pelvis and becoming especially hyperemic in a condition of colon stasis and constipation. Men past middle life with a history of no specific infection, who are heavy eaters, who take no regular exercise and with a blood pressure usually above normal, may be harboring a condition of colon stasis in which cases there is a tendency to low grade generalized infection from the colon of the pelvic organs and especially the prostate. Some of the newer effective methods of treatment of nonspecific as well as specific cases are iodized autoserum, intramuscular, soluble iodin intravenously and the local and general diathermy fever heat treatments.

The Incidence of Gall Stones and Gall Bladder Disease.—CRUMP (*Surg., Gynec. and Obst.*, 1931, **53**, 447) states that in the study of material from 1000 routine autopsies at the City Hospital in Vienna, the following facts were brought to light: 450 were males while 550 were females. Eighty-seven and one-tenth per cent of the individuals were over 30 and 77.9 per cent were over 50 years of age. Gall stones were present in 32.5 per cent of the cases. These were present in 37.8 per cent of the females and 26.2 per cent of the males. Twenty-five per cent of the individuals were affected after the fourth decade and 50 per cent after the seventh decade of life. Inflammatory or common gall stones

made up 73 per cent of the stone cases. Cholecystopathy occurred in 59.6 per cent of all cases and affected males in 58.4 per cent and females in 60.2 per cent. With the advance of the decades the case incidence increased from 20 per cent in the first age group to 77.6 per cent in the eighth decade of life. Chronic pericholecystitis was the most frequent pathologic condition and chronic cholecystitis was next in frequency. Primary carcinoma of the biliary tract occurred in 26 instances—7 males, 19 females—in which stones were present in all but 4 cases. In 2 cases the growths were primary in the ducts. Cholesterosis of the gall bladder was present in 36.8 per cent of all cases. Males were affected in 35.8 per cent and females in 37.7 per cent of the cases. This condition was very frequent in the early decades and maintained a more or less constant average throughout the age groups. Pathologic conditions were present in 41.3 per cent of all cases. There was an increase in incidence of disease with the advance of the decades. The most frequent finding was dilated ducts in 50.8 per cent and next frequent a lacerated papilla of Vater in 47.7 per cent of the abnormal findings. Gall stones were found in the bile ducts in 78 cases, which is 24 per cent of the cases with cholelithiasis. This finding was not affected by the age of the individual so that any patient with gall stones has one chance in four of having stones in the bile ducts.

Malignant Changes Occurring in Benign Giant-cell Tumors of Bone.—Simons (*Surg., Gynec. and Obst.*, 1931, **53**, 469) says that amputation cures 100 per cent of the cases of giant cell tumor. Resection or complete excision can be expected to cure 100 per cent of the cases. The only patient dying of the disease treated in this manner had no local recurrence, which is all that can be expected of the operation and there is also some doubt as to the correct diagnosis in this case. Curetting cures 63 per cent of the cases. Combined with other treatment, as radiation, 72 per cent; radiation treatment alone cures 75 per cent of the cases. Treatment by Coley's toxin cured 42 per cent of the cases. Of the cases of accepted benign giant-cell tumor treated conservatively, 7.5 per cent died, presumably of metastases. In 3 cases in which it was possible to compare microscopic sections of the tumor first treated with that causing death, the character of the growth had changed from benign to malignant. There is no proved instance in the cases of giant-cell tumors in the Registry of Bone Sarcoma registered before 1925 of a tumor of this type causing death from metastases. There is definite evidence, however, that a benign giant-cell tumor may change its character and become an osteogenic sarcoma causing death. Uncontestable data are difficult to obtain but this change is known to have occurred in 3 cases in this series, 3.7 per cent.

Retroperitoneal Tumors.—Cohn (*Arch. Surg.*, 1931, **23**, 655) claims that retroperitoneal masses may be present and yet remain undetectable during life by any available diagnostic methods. The Roentgen evidence of extrinsic obstructive intestinal phenomena is interesting and diagnostic when present, but the absence of such a sign is by no means acceptable as evidence that a retroperitoneal growth does not exist. Retroperitoneal tumors sometimes move with respiration, thus making it difficult if the mass is on the left side to eliminate splenomegalia.

The symptoms caused by a retroperitoneal growth are dependent on the location of the growth. Proximity to the celiac plexus causes digestive phenomena, whereas growths even of larger size in other locations may not cause digestive disturbances. Digestive disturbances are not diagnostic as they are present in so many conditions other than retroperitoneal tumors. Anemia is present in many cases of retroperitoneal growths but is not to be relied on as a diagnostic phenomenon. Anemic and digestive disturbances may mislead one to treat the patient for an entirely different condition. Edema of extremities and ascites are present when the growth is large and when it is so situated as to interfere with the venous return. A growth situated on the right side readily produces edema, whereas a large growth on the left side may not be associated with edema of the lower extremities or ascites. Retroperitoneal masses may be associated with chylous ascites and chylous pleural effusions. Retroperitoneal sarcomas may be primary and productive of metastases, whereas other retroperitoneal sarcomas may be secondary growths. When searching for the primary cause of retroperitoneal metastases, teratoma of the testicle must not be overlooked as a possible source.

THERAPEUTICS

UNDER THE CHARGE OF

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AND

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The Action of Digitalis on the T Wave of the Electrocardiogram.—Recently the inversion or flattening of the *T* wave of the electrocardiogram commonly accepted by American authors as being a fairly constant manifestation of the action of digitalis has been brought into question, particularly in Europe. COELHO (*Arch. d. mal. du cœur*, 1931, **24**, 746) reviews the more important literature on the subject and presents the results of his own carefully controlled observations upon man. He employed digitan (digipuratum) in varying doses in a group of 22 patients with cardiac disease. Whereas others have found inversion of the *T* wave to occur in as much as 90 per cent of patients receiving adequate doses of digitalis, the author obtained inversion in only 18 per cent of his cases. He also found that the inversion bore no necessary relation to the total dose of digitalis taken, the phenomenon occurring as well with moderate doses as with those which were extremely large. He calls attention to the fact that inversion of the *T* wave is a fairly frequent occurrence in the presence of chronic myocardial disease, myocardial infarction and occasionally in apparently normal hearts due to some undetermined factor. From his studies he believes that

this alteration in the electrocardiogram cannot be regarded as a characteristic manifestation of digitalis action and, furthermore, that it is not a safe guide for the control of digitalis administration. He suggests that in those cases in which it appears it is due to certain conditions associated with chronic myocardial disease which may be brought to light as a result of digitalis action rather than being due primarily to the actions of the drug itself.

The Treatment of Agranulocytosis With Roentgen Ray Irradiation and Blood Transfusion.—Opinions regarding the effect of Roentgen ray irradiation of the long bones in agranulocytosis are somewhat contradictory. HARTWICH (*Klin. Wchnschr.*, 1932, **11**, 104) used repeated Roentgen ray treatment in 3 cases of agranulocytosis. The beneficial effect of the treatment in these cases manifested itself in a temporary rise in the white cell content of the blood. Definite permanent improvement, contrary to the experience of Friedemann, was not observed. There are several reports in the literature which claim that blood transfusion is beneficial in this condition. Blood transfusion was used in 6 patients. In each instance the author claims there was a prompt clinical improvement. The temperature subsided with crisis or with lysis, and at times there appeared a most astonishing improvement in the necrotizing process of the throat. There was also an increase in the white cell count. This, however, was not always permanent. The author observed repeatedly that the general clinical improvement, the fall in temperature and the healing of the ulcerated mouth lesions were quite independent of the number of white blood cells. The author advocates the more frequent use of blood transfusion in the treatment of agranulocytosis.

The Treatment of Ulcus Cruris.—Among the numerous therapeutic agents used in the treatment of chronic ulcers of the lower extremities, KUN (*Münch. med. Wchnschr.*, Jan. 1, 1932, vol. **26**) claims that "lyssia salve" is most effective. The composition of this salve is as follows: Zinc oxidat. amyl., 15 gm. āā; vasel fl., 35 gm.; naftalan, 16 gm., balsam Peruv., 6 gm.; chinolin sulph., 0.5 gm.; ichthyol, 1 gm.; extr. hamam. fl., 3 gm.; oleum cacao, 3 gm.; bism. oxyiodogall., 1 gm.; adeps lanæ ad. 100 gm. The ulcer is cleaned with benzine and covered with the salve in the morning. Within a day or two there is evidence of healing and within a short period granulation tissue fills in the ulcer. In ambulatory patients a bandage is applied following the application of the salve and removed 4 to 5 days later.

The Beneficial Effect of Calomel in Rheumatic Endocarditis and Pancarditis.—It is often not appreciated that calomel was used as a diuretic as early as the eighteenth century. MacKenzie has pointed out again that certain cardiac patients who do not respond to digitalis will show diuresis after the administration of calomel. PAUL and BABATZ (*Münch. med. Wchnschr.*, January 1, 1932, vol. **25**) administered repreated doses of calomel in amounts of 0.2 to 0.3 gm. (3 to 5 grains) to patients who were suffering from repeated attacks of fever, valvular damage, cardiac enlargement, congestive failure of the circulation and anemia. The authors claim that in every case there was

subjective and objective improvement. They do not offer any explanation for the mechanism of action of calomel. In order to avoid nephritis the water balance was carefully followed. In the presence of casts in the urine calomel was not administered. The bowels were kept open before its administration. Under these conditions no kidney damage was observed. It is claimed that similar improvement was not observed after salyrgen or after mercurial preparations combined with proteins.

PEDIATRICS

UNDER THE CHARGE OF
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The Mechanism of Hemophilia in Infancy and in Childhood.—KUGELMASS (*Am. J. Dis. Child.*, 1932, **44**, 50) feels that criteria necessary and sufficient for the diagnosis have been formulated on the basis of experimental and clinical studies. It has been shown by a study of the constituents involved in blood coagulation that the hemophilic deficiency occurs in the primary stage of the blood-clotting mechanism. Hemophilic blood shows a strikingly low prothrombin content compensated by a correspondingly high antithrombin content. The platelets are normal in number but are physiologically defective, having a slow rate of disintegration. Hemophilic blood is characterized by a blood-clotting index that is less than one-tenth of normal. The index constitutes the ratio of the concentration of the substances tending to clot over those tending to favor bleeding. The normal index of clotting function is 0.5, whereas the hemophilic clotting index is less than 0.05. This very low index of blood-clotting is diagnostic of hemophilia. The index of blood-clotting function shows a great increase after transfusion, but the improved index last for only 48 hours. Transfusion does not alter the clotting function of blood in hemophilic subjects with manifestations in the joints. Dietary protein, lipids, vitamins and minerals do not alter the deficient blood-clotting function in hemophilia. Hemophilic individuals show the absence of the female sex hormone in their tissues normally present in males. Ovarian therapy, theelin and other products of the female generative organs injected into the hemophilic subject produce no change in the clotting mechanism evaluated quantitatively. Serum injected or applied locally is not effective in controlling hemorrhage in hemophilia, unless it is fresh and rich in thrombin. Nonhemophilic bleeders respond readily to any serum and to dietary protein therapy.

Iron in the Liver and in the Spleen After Destruction of Blood and Transfusions.—GLADSTONE (*Am. J. Dis. Child.*, 1932, **44**, 81) examined a series of livers of fetuses and infants obtained at autopsies. He studied these microscopically and chemically to determine the variations in the amounts of iron present and the factors on which such variations depended. There was no evidence microscopically or chemically of large or progressive depositions of iron in the liver during the last 4 months of intrauterine life. Exclusive of iron as hemoglobin, the entire liver

of the mature new-born infant contains on the average about 32 mg. of iron. The largest amounts of iron were found in the liver from 1 to 10 weeks after birth, and these were believed to depend on postnatal intravascular destruction of blood. Hemosiderosis of the liver may also result from hemorrhages into the tissues or cavities of the body of the fetus or infant, and during fetal life it may result from similar hemorrhages in the mother, the liberated iron reaching the fetus through the placenta. Hemosiderosis of the spleen and the liver follows transfusion of blood. The amount of iron found in the liver is influenced by the size and the frequency of the transfusions. The appropriation and utilization of transfused blood was studied. It seems that in human beings at least part of the transfused blood is quickly phagocytosed. The red cells are physically disintegrated and chemically digested within the phagocytes, and the products are liberated into the blood stream. Among these products are bilirubin and iron derived from the hemo portion of the hemoglobin, and the poorly known but extremely important derivatives of the globin portion of the molecule. These studies indicate that in large amounts iron as well as bilirubin is taken up from the blood stream by the hepatic cells. It has been demonstrated also that the kidney removes large quantities of urobilin under these circumstances. The kidney has the power also of taking up iron from the blood stream after extensive destruction of blood, and this iron may be found in the urine.

The Effects of Parathormone and Ammonium Chlorid on Bones of Rabbits.—JAFFE, BODANSKY and BLAIR (*J. Exp. Med.*, 1932, **55**, 695) found that a very large single dose of parathyroid extract produced rapid and extensive decalcification of the bones of a young rabbit. Gradually increased doses of the extract failed to produce significant changes in the young and fully grown adult rabbits. Ammonium chlorid, administered by the stomach tube, was without effect on the bones when given to rabbits treated with the extract or to otherwise untreated rabbits. Calcium lactate did not promote the appearance of signs of overdosage of parathyroid extract in rabbits during treatment, nor were metastatic calcifications observed in the soft tissues after termination of the experiment. The rabbit is highly resistant to the decalcifying effects of gradually increased doses of parathyroid extract, and is therefore not satisfactory material for experimental studies of bone changes of chronic hyperparathyroidism. The appearance of actively transforming bones of a young growing rabbit, particularly at the site of rapid growth, is not to be confused with the more severe fibrous processes produced by parathyroid extract in guinea pigs, dogs and rats.

Progress in the Nutrition of Infants.—DURAND (*J. Am. Med. Assn.*, 1932, **99**, 275) summarizes the essential points of the problem of infant feeding. The casein curd of cow's milk must be modified. To do this efficiently boiling and acidification are employed. The question of buffer substance is not of the greatest importance. The use of accessory food factors not only prevents rickets, its resultant deformities and the more fatal tetany, with scurvy, xerophthalmia and the other forms of avitaminoses, but also incidentally improves the resistance of the infant to infection. It is recognized that hunger is the greatest danger of the

infant and the younger child the greater is the danger. The use of the cereal waters and very weak formulæ weaken the baby and render it more liable to infections. The early broadening of the diet is now generally accepted. In general the best guide to the optimal proportions is that of breast milk in which protein, fat and carbohydrate are found in the percentages of 1, 3.5 and 7. There is a growing tendency to reduce the amount of milk in infant feeding. Limitation of the total quantity of fluid must be considered. Except during periods of excessive heat or during fever or watery diarrhea, the infant does well on one-fifth of its body weight of fluid daily during the first weeks, one-seventh at 6 months, and one-eighth up to the first year. If fluids are kept near this level, less vomiting occurs, the bottle is more readily emptied, the bed and clothing are not so constantly water-soaked, the insulation against changes in surrounding temperature is consequently better and the skin is less irritated.

Celiac Disease.—HAAS (*J. Am. Med. Assn.*, 1932, **99**, 448) states that there are a constitutional tendency to the disease and a characteristic intestinal flora. There appear to be a faulty absorption and utilization of carbohydrates and fats. The fats are of secondary importance, for if strict attention is paid to the carbohydrate intake, tolerance of fats follows. A flat blood sugar curve is probably pathognomonic of active celiac disease. The successful treatment of celiac disease requires a high protein diet, of which the basis is protein milk, to which is added carbohydrate in the form of ripe banana powder and ripe banana, although other fruits and some vegetables are tolerated in some degree. The author claims that no nutritional relapses occur with this diet. A relapse not due to an acute infection is always due to the introduction of some carbohydrate other than that of banana, or rarely due to some intolerable fat. The banana contains all vitamins except vitamin D. It hydrolyzes starch and transforms the intestinal flora and produces starch-free alkaline stools. Vitamin D must be used as the concentrate viosterol and not as cod liver oil, and for the anemia accompanying celiac disease some form of iron must be given. The prognosis in cases of celiac disease under this treatment is excellent, and the patients attain full stature and are capable of using a normal diet.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Reactions Following the Administration of the Arsphenamins and Methods of Prevention.—IRELAND (*Am. J. Syph.*, 1932, **16**, 22) reviews the record of 2100 patients receiving arsphenamins for the treatment of syphilis and reaches the following conclusions as to the incidence

and type of reactions noted: 11.2 per cent of the patients showed various symptoms of intolerance to the arsphenamins, the most common type being of gastrointestinal origin. Old arsphenamin was much more reaction-producing than neoarsphenamin. Of the reactions observed, 72 per cent occurred early in the course of treatment between the first and tenth injections although no particular type of syphilitic involvement appeared to predispose to intolerance. The probability of reaction appeared to be twice as great in females as in males. The author believes that reactions can be very largely controlled by the complete physical appraisal of the patient before the institution of treatment, the introductory use of iodid and mercury in patients with syphilitic visceral involvement, the recognition of the importance of conservative dosage, slow administration and adequate dilution in preventing reactions, and finally such adjuncts as the preliminary injection of atropin or adrenalin, ephedrin by mouth, calcium gluconate intramuscularly and vehicles other than distilled water. The author's review of the literature reveals a very diversified list of reactions but he points out that the number of severe or fatal reactions is low when the large number of patients under treatment is considered.

Unusual Clinical Manifestations Following Intravenous Administrations of Gold Compounds.—THRONE, KINGSBURY and MYERS (*Arch. Dermat. and Syphilol.*, 1932, **25**, 494), on the basis of their own experience as well as that recorded in the literature, review the wide range of toxic reactions encountered after the intravenous use of gold compounds in lupus erythematosus, tuberculosis cutis and the tuberculids. These reactions have already been summarized in the review of Driver and Weller's article, which appeared in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES for October, 1931. The present authors offer the following suggestions to prevent the untoward effects of gold administration: (1) The patient should be examined for focal infections which, if found, should be removed prior to the institution of gold therapy. (2) A preliminary analysis of the blood should be made to determine the possible presence of a high sugar and low chlorid content which demands a preliminary course of injections of sodium thiosulphate. In cases showing a high blood sugar content not associated with pancreatic deficiency or metallic retention, the doses of the gold compound should be comparatively small. Patients with definite diabetes, however, seem to tolerate treatment with gold preparations. (3) The first sign of intolerance, as manifested by dryness of the mouth and pruritus, is an indication for discontinuance of the gold compound and the use of sodium thiosulphate. In the authors' experience, these symptoms are invariably accompanied by an increase of the blood sugar, a decrease in the chlorids and frequently by a marked decrease in the urea nitrogen. (4) Chemical examination of the blood at weekly intervals for the foregoing changes may enable one to foresee an intolerance to gold which can be prevented by proper eliminative treatment. (5) The initial dose of a gold compound should be small, not exceeding 25 mg. This dose can be increased if well borne and relatively noneffective, but the dose should be kept low if the clinical response is satisfactory. (6) Positive contraindications for gold therapy are marked hepatic and renal disturbances, pregnancy, lupus erythematosus disseminatus acutus, and elevation of temperature.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Surgery of Pelvic Sympathetic Nerves.—The surgery of the sympathetic nervous system has received an unusual amount of attention in recent years, and from the reports in the literature the results of many of these operations have been well worth while. The gynecologists must now interest themselves in this subject, at least from the theoretical standpoint, since the work of FONTAINE and HERRMANN (*Surg., Gynec. and Obst.*, 1932, **54**, 133) of Leriche's Clinic in Strasbourg indicates that there may be a fertile field for this type of surgery in relieving certain pelvic disorders in women. The latter investigators believe that the hypogastric plexuses carry the important pathways of sensation from the internal genital organs to the medullary centers and that the section of the superior hypogastric plexus (presacral nerve) above the hypogastric ganglion is a safe, simple and efficacious way of interrupting these pathways in the treatment of the functional type of dysmenorrhea as well as a method of relieving other forms of severe pelvic pain. The cases in which pelvic sympathectomy is indicated, according to their views, can be divided into three main groups: Group A: Those cases in which no organic lesion of the genital organs can be found to account for the pelvic pain, *i. e.*, functional dysmenorrhea. Group B: Those cases with slight pathologic processes in the pelvis which do not react favorably to ordinary gynecologic treatment, *i. e.*, sclerocystic degeneration of the ovaries or persistent pelvic pain following some previous operation. Group C: Those cases in which the pathologic lesion is known but which has been found to be too extensive for surgical removal, *i. e.*, inoperable neoplasms in the pelvis giving rise to severe pain. They have performed resection of the superior hypogastric plexus for the relief of severe pelvic pain in 22 patients. Six of the patients have failed to return for follow-up examination, but at the time of discharge from the hospital they were completely relieved of their pain. One patient died on the second postoperative day, while 13 of the 15 patients that have been followed have been relieved of all pelvic and abdominal pain for periods of time up to 4 years. Two patients have had only slight or no benefit from the operation. The technique of the operation as they describe it is quite simple. With the patient in the Trendelenburg position, the small intestines and colon are packed upward toward the diaphragm and the rectosigmoid is retracted toward the left. The promontory of the sacrum and the two common iliac arteries are then located. The posterior parietal peritoneum is then incised at a point just above the promontory of the

sacrum and directly in the midline. Immediately beneath the peritoneum and anterior to the midsacral artery will be found the nervous filaments which constitute the superior hypogastric plexus. In very thin women these fibers can be seen through the peritoneum, while in obese women the plexus is usually embedded in adipose tissue. If the mesosigmoid is short, care must be taken not to injure the inferior mesenteric vessels. Frequently several nerve fibers are densely adherent to the right iliac vein. After all the filaments have been isolated, a segment, at least 1 inch long, should be resected from each main nerve fiber in order to prevent any possible regeneration. The posterior peritoneum is then closed by a continuous catgut suture. While it is appreciated that the Strasbourg school is perhaps unduly enthusiastic about the surgery of the sympathetic nervous system, it would seem that this procedure might be well worth while trying in some of the patients who have such intense dysmenorrhea and have been unrelieved by all other treatment except hysterectomy. (Especially indicated in certain carefully selected cases of incurable cancer in whom other methods fail to relieve pain.—C. C. N.)

OPHTHALMOLOGY

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The Influence of Pregnancy on the Visual Field.—JOHNS (*Am. J. Ophthal.*, 1930, **13**, 956) reports the results of her examinations of the fields of vision of 29 young women in the course of essentially normal uncomplicated pregnancies. Only 1 of these patients showed any definite evidences of pituitary dysfunction. With one possible exception, none of them showed any diagnostic changes in the preoperative and postoperative rays of the sella turcica. The visual fields were studied at rather frequent intervals in the prepartum period of observation and were checked postpartum. In about 80 per cent of the patients a definite tendency to concentric contraction of the form and color fields was found. This tendency was most marked in the last four weeks of pregnancy and increased up to the time of delivery. The fields tended to return to normal after delivery. In 20 of the 29 patients the blind spots were enlarged. A characteristic pituitary type of field was not found in any case. The author believes that these field changes are secondary to a general reduction of retinal vitality which is part of the general lowered vitality of the pregnant state and that they are not due to enlargement of, or vascular changes in, the pituitary gland.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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A Study Concerning the Incidence of Streptococcus Epidemicus.—The occurrence of septic sore throat and of carriers of Streptococcus epidemicus during interepidemic periods has become a matter of importance. Inasmuch as southern California has never had an epidemic of septic sore throat, BONYNGE (*Proc. Soc. Exper. Biol. and Med.*, 1931, **28**, 991) over a period of 4 months conducted a series of Streptococcus epidemicus among certain groups of persons in Los Angeles. From the throat swabs of 250 apparently healthy employees, Streptococcus epidemicus was recovered from 7 individuals, none of whom had had septic sore throat and all of whom had hypertrophied tonsils—a percentage of 2.8 for the "carrier group." Of 66 persons presenting themselves for removal of hypertrophic tonsils, Streptococcus epidemicus was isolated in 6 (9 per cent). In 2 children otitis media and subsequent mastoiditis was found to be of Streptococcus epidemicus origin. In all, 18 strains of Streptococcus epidemicus were recovered; 5 from persons suffering from acute infections and 13 from human carriers. The author's results are not widely variant from those obtained in Chicago by Pilot and Davis (*J. Infect. Dis.*, 1930, **47**, 503).

RADIOLOGY

UNDER THE CHARGE OF
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Roentgenologic Study of Intrathoracic Lymphoblastoma.—Sixty-seven cases of intrathoracic lymphoblastoma, comprising 40 cases of Hodgkin's disease, 17 of lymphosarcoma and 10 of leukemia were studied by KIRKLIN and HEFKE (*Am. J. Roent. Ray and Rad. Therap.*, 1931, **26**, 681). In the opinion of the writers, roentgenologic examination of the thorax in cases of Hodgkin's disease, lymphosarcoma and leukemia does not permit a precise diagnosis of any one of these diseases. They must be considered as one group which might be called either lymphoblastoma or malignant lymphoma. Demonstrable roentgenologic manifestations in the thorax may be expected in about 50 per cent of the cases of Hodgkin's disease, and in about 20 per cent of the cases of lymphosarcoma or of leukemia. In the series reported, enlargement of the mediastinal and hilar nodes was the most common manifestation. Involvement of the lungs, either of the infiltrative or metastatic type was found in 30 per cent of the cases of Hodgkin's disease, in about 23 per cent of the cases of lymphosarcoma and in 40 per cent of the cases of leukemia whenever intrathoracic involvement was demonstrable.

Roentgen Ray Pelvimetry—A Simplified Stereoroentgenographic Method.—A method of pelvimetry by stereoroentgenography is described in considerable detail, with illustrations and explanations of each of the three stages, by HODGES and LEDOUX (*Am. J. Roent. and Rad. Therap.*, 1932, **27**, 83). No special professional ability is required of the person making the films, and the apparatus may be used not only for pelvimetry but for practically any type of Roentgen examination.

Hepatography and Lienography Following the Injection of Thorium Dioxid (Thorotrast).—In order to demonstrate the shadow of the liver and spleen roentgenologically, STEWART, EINHORN and ILLICK (*Am. J. Roent. and Rad. Therap.*, 1932, **27**, 53) have tried the injection of thorotrast in 8 cases. The drug is supplied in ampules, each containing 3 gm. of thorium dioxid suspended in 12 cc. of water. The mixture was injected intravenously and very slowly, and a second ampule, or more, was given next day or the second day after. The material was well tolerated up to an hour after injection in all cases. Five had no definite after effects. Three had vomiting attacks for several days after the injection and 2 patients had hemorrhages. Subsequently 7 of the 8 patients died, but no death was directly attributable to the drug. No increase in density of the liver and spleen occurred until after 24 hours, and the maximum density was reached in 1 or 2 weeks. A dense shadow of the liver was obtained in all patients except 1 who died shortly after. In 1 case the shadow of the liver was mottled; the diagnosis of malignant disease was confirmed at operation. In 7 cases the spleen was also demonstrable; the shadow varied in intensity and in a few instances was quite dense.

Radium as an Adjunct to Surgery in the Treatment of Carcinoma of the Fundus of the Uterus.—BOWING and FRICKE (*Am. J. Roent. and Rad. Therap.*, 1931, **26**, 738) relate their experience with 189 cases of carcinoma of the fundus, 172 of which were traced. Of the 189 patients, 87 were treated by operation and irradiation, and 102 were treated by irradiation only. The late results in a few favorable cases in which irradiation alone was used compare favorably with the results obtained by operation alone. The authors regard irradiation as an invaluable adjunct to surgery. Irradiation alone yields high returns in palliation but poor remote results, mainly because the majority of lesions are too advanced to permit adequate treatment.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Regenerative Possibilities of the Central Nervous System.—GERARD and GRINKER (*Arch. Neurol. and Psychiat.*, 1931, **26**, 469) feel that there is "good evidence of spinal regeneration in amphibia and other

lower vertebrates" as well as the reported evidence of regeneration of the optic nerve in adult rats and spinal regeneration in birds and mammals in literature. They present a series of experiments on newborn rats and rat fetuses *in utero* in which the spinal cords were transected by a single clean cut with a cataract knife, and subsequently studied histologically. "Many experiments yielded negative or no results because the animals died or the true spinal column became displaced. Several rats operated on at birth, however, gave evidence of a gradual return of function. One animal, studied with special care, which showed evidence of a complete section at the time of operation, was entirely paralyzed and anesthetized below the lesion for 2 weeks, while in a subsequent 3 weeks the recovery of sensation and voluntary sensation and motion was practically complete. The spinal cord of this animal showed no evidence of a lesion. Several rats operated on *in utero* were born from 5 days to 1 week later with the sense of pain, voluntary motion or both present in the hind quarters. The spinal cords showed partial lesions or none at all." The authors consider the possibilities of the growth of nerve fibers into and across a lesion after complete or partial transection of the spinal cord is definitely established.

The Cerebral Lesions in Purulent Meningitis.—WERTHAM (*Arch. Neurol. and Psychiat.*, 1931, **26**, 549) presents a histologic study of the cerebral parenchyma of 24 cases of purulent meningitis. Apart from the changes of an encephalitic and toxic degenerative type, he noted other lesions of the nervous parenchyma. These lesions were chiefly in the cortex, but subcortical structures such as the basal ganglia were also affected, especially in children. He found for most of the lesions a circulatory basis as the chief factor in their production with toxic factors playing a subordinate part. If a full-fledged encephalitis supervenes the infection does not progress from the outer and ventricular surfaces, but the encephalitis attacks the central parts of the substance of the brain like an independent process. Therapeutic procedures directed toward relief of the circulatory system, the author feels, are necessary in purulent meningitis.

The Choroid Plexus as a Dialyzing Membrane: I. Observations in Experimental Hydrocephalus.—HOEN (*Arch. Neurol. and Psychiat.*, 1931, **26**, 496) presents a study of experimental hydrocephalus produced in 18 days by obstruction of the aqueduct of Sylvius. The experimental work involved: (1) Alterations in the volume of the spinal fluid, and (2) alterations in its salt content. "The former caused only transient changes in ventricular pressure, whereas within the time limit of the experiment the latter caused permanent changes." This observation is possibly of clinical importance in cases which require spinular ventricular tapping for relief of pressure.

Family Periodic Paralysis: Report of a Case.—ZABRISKIE and MCDONALD (*Arch. Neurol. and Psychiat.*, 1932, **27**, 220) present the case of a man, aged 23 years, who had suffered intermittent attacks of flaccid paralysis since the age of about 7 years. The onset of the attacks was nearly always at night, beginning with a numb feeling in the back of the neck, followed by weakness of the legs, then of the trunk,

then of the arms, and finally of the muscles of the neck. In severe attacks there was virtually complete paralysis of all the muscle groups mentioned. There was no involvement of the cranial nerves. The paralysis was flaccid, with decrease or loss of the deep reflexes. The attacks lasted from 2 to 24 hours. There was considerable sweating at the beginning and end of an attack. A systolic murmur, with enlargement of the heart to the left, occurred in several of the more complete attacks. Electrocardiograms gave negative results. All laboratory studies were negative. A partial attack, *viz.*, that of one forearm, could be induced by local cooling. The patient's mother had suffered from the same disease and died during an attack of paralysis at the age of 23 years.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
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Malignancy in the Lung, Including 8 Primary Carcinomas With Autopsy Findings.—Eighty-one cases of malignant tumors of the lung have been reviewed by MOSES (*Am. J. Int. Med.*, 1931, **5**, 765). Of these, 8 have proven primary carcinomata of lung at autopsy. Thirty-five cases were considered clinically as primary carcinoma of lung, postmortem examination not having been made. Secondary carcinoma of lung occurred in 20 cases of this series, metastatic lymphosarcoma in 10 and metastatic sarcoma in 6. One case of secondary hypernephroma and 1 of teratoma were also encountered. Of carcinomata that metastasize to lungs, breast and kidney tumors are considered the most important. Histologically three types of pulmonary carcinoma are recognized—those from bronchial epithelium, from bronchial mucous glands and from alveolar epithelium (bronchogenic or parenchymatous). Carcinoma from bronchial epithelium often causes bronchial obstruction but seldom a diffuse tumor of lung. Those from glands usually arise in the larger bronchi while those from alveolar epithelium produce infiltrating and often rapidly spreading tumor masses involving large areas and frequently resembling organizing pneumonia. The commonest symptoms encountered were cough, with or without sputum, hemoptysis, dyspnea, pain either constant or paroxysmal, cyanosis, weakness and emaciation. The author calls attention to the fact that the occurrence of an unexplained pleurisy, especially a pleurisy with an effusion, in a patient in middle or later life should suggest the presence of a new growth in lung or mediastinum.

Enzoötic Hepatitis or Rift Valley Fever.—DAUBNEY and HUDSON (*J. Path. and Bacteriol.*, 1931, **34**, 545) describe a new virus disease which made its appearance as an epizoötic of serious proportions in a large colony of sheep in the Rift Valley, Kenya Colony, East Africa.

The outbreak was carefully investigated, both as to pathology and bacteriology. Sheep, cattle, goats and man are susceptible. The mortality is over 95 per cent in very young lambs, but is low in adult sheep and cows and practically *nil* in man. There is a marked tendency for pregnant ewes and cows to abort during the course of the disease. In man there is but a slight transient fever often accompanied by joint pains. The characteristic lesion found in animals dead of the disease is a liver necrosis which is strikingly similar to that of yellow fever. (KLOTZ and BELT, *Am. J. Path.*, 1930.) Both cytoplasmic and nuclear "inclusion bodies" occur in the affected liver cells. The virus is a filter passer and there is evidence to show that it is transmitted by a mosquito (Tæniorhynchus brevipalpis). It is suggested that the disease falls into the same group as yellow fever and dengue. (Editorial, *Lancet*, October 3, 1931, p. 751.)

Melanosis Mucosæ Appendicis Vermiformis.—LILLIE (*Am. J. Path.*, 1931, **7**, 701) reports melanotic pigmentation of varying degrees present in 266 out of 750 human appendices examined. The condition is of a nature similar to melanosis coli escribed by PICK (*Berl. klin. Wchnschr.*, 1911, vol. **48**). The pigment lies in cells of a macrophage or fibroblastic type immediately beneath the mucosal epithelium. The pigmentation increases with age but is unrelated to race, sex or occupation. It is infrequently demonstrable in appendices which are the seat of active inflammation. Dilatation or atony of the appendiceal wall is correlated with an increased frequency and intensity of the pigmentation.

A Case of Myeloma With Unusual Amyloid Deposition.—PAIGE (*Am. J. Path.*, 1931, **7**, 691) presents a case of multiple myelomata in which there occurred tumorlike masses of amyloid in the muscles about the shoulder girdle. There was also a heavy deposition in nearly all organs and tissues of the body except the liver. All the usal staining reactions for amyloid were positive. Bence-Jones protein was present in the urine. The author is able to find in the literature reports of 3 other cases of multiple myelomata accompanied by amyloidosis. He favors Well's suggestion that the deposit may be a "consolidation of the Bence-Jones protein."

Etiology in Influenza.—LISTON (*Glasgow Med. J.*, 1930, **113**, 64) believes that Pfeiffer's bacillus is not a normal saprophyte of the air passages and that the abandonment of this organism as the causal agent in the disease by many bacteriologists is due to failure to use suitable media for isolations and to confusing microörganisms found in normal throats with Bacillus influenzæ proper. While numerous reports, in recent years, have described the almost constant finding of organisms culturally identical with Bacillus influenzæ in the throats of normal individuals, it should be remembered that the identity of these has not been clearly proven as the only method at present available for identification of the hemoglobinophilic bacteria is their nutritional relationship to hemoglobin. The author states that he generally can distinguish members of this group from the true Pfeiffer bacillus by sugar fermentations. Should further study show that this is a reliable method of subdivision then considerable advance will have been made in our knowledge of these bacteria and their etiologic significance in influenza.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Oral Immunization Against Pneumococcus Types II and III and the Normal Variation in Resistance to These Types Among Rats.—Ross (*J. Exp. Med.*, 1931, **54**, 875) found considerable variation in the resistance of different rats toward Type II pneumococcus. In general, older rats survive much greater doses than young ones, illustrating the acquisition of a natural partial immunity. The same is true for Type III but the immunity appears somewhat later in life and does not reach the same height. An active immunity can be created against Types II and III in rats by feeding the dead organisms or the Berkefeld filtrate of the bile salt-dissolved cells. This immunity resembles that obtained against Type I in several respects. *The Rôle of the Soluble Specific Substance in Oral Immunization Against Pneumococcus Type I.*—In further experiments (*Ibid.*, p. 899) it was found that feeding the purified soluble specific substance of Type I pneumococcus protects rats against an intraperitoneal injection of the virulent organism. This increased resistance resembles that obtained when the intact (dead) or dissolved bacteria are fed, as follows: (*a*) One feeding is sufficient; (*b*) the interval between the feeding and the appearance of the immunity is the same; (*c*) the duration is approximately the same; (*d*) when the immunity is exhausted it can be renewed by a new feeding; (*e*) the immunizing action is type specific. The differences between the effects of feeding the purified specific substance and the intact or dissolved organism to rats appear to be quantitative rather than qualitative, the proportion of animals protected and the height of the immunity being generally, though not always, less in the case of the former. In contrast to the immunizing action which the soluble specific substance possesses when administered to rats, feeding it to mice failed to protect them. Neither were mice definitely immunized by parenteral administration. A sodium glycocholate solution of pneumococcus Type I lost part of its immunizing activity on standing for 1 year. The failure to immunize mice and the loss of activity of the bile salt solution of pneumococcus, on standing, are discussed in terms of (*a*) the possible presence of a second cell constituent which is active by mouth and (*b*) a possible intramolecular change in the type-specific polysaccharid associated with a loss of immunizing action while retaining the precipitin reaction.

The Movements of Epidemic Meningitis, 1915–1930.—HEDRICH (*Pub. Health Rep.*, 1931, **46**, 2709) discusses the subject in detail and presents the following summary: This paper reviews some of the general epidemiologic characteristics of epidemic meningitis, and the recent movements of the disease as to time and place: (1) The available

evidence indicates that during epidemics surprisingly large proportions of the population may at one time or another become infected with the meningococcus. Under highly congested conditions, as in army camps, it appears that practically the entire population may become infected once or oftener during epidemics. Probably far less than 1 per cent of such infections result in clinical attack, as annual attack rates in excess of 1 per 1000 population are rare. The case fatality, however, is heavy; approximately half of the reported cases died during the recent epidemic, in spite of fairly widespread use of serum. (2) Meningitis became increasingly prevalent in Europe shortly after the opening of the World War, and in the United States shortly after her entry, when mobilization began. The highest attack rates in England came in 1915, and in the United States in 1918. In 1928–1930 the disease was again epidemic in most part of the world. (3) The interval between the last two epidemic maxima was 11 years in the United States, and a few years longer in most European countries. The interepidemic interval is highly variable. It has oftenest been 6 to 12 years, but some areas have run as long as 25 years without epidemics. Massachusetts, for example, has had no appreciable epidemic since about 1905, and New York City only a minor one, namely, in 1928–1930. (4) Over broad areas, such as large groups of states, epidemics have appeared, not as sporadic explosions but as crests of rather smooth and systematic wave, the rise and declining phases of which have covered a period of 3 to 6 years or longer. Within smaller areas, such as individual cities, the movements of the disease have been less systematic. (5) Neither of the last two epidemics was synchronous in different parts of the United States, some regions having lagged 2 years behind others. The time rate of epidemic development within specific areas, and the rate of geographic movement are very much slower for meningitis than for influenza. (6) In the 1918 epidemic the reported attack rates were highest in the southern sections, probably due to the large number of military concentration camps; the Rocky Mountain states had the lowest rates. In the 1928 outbreak the southern states had the lowest and the mountain states the highest rates.

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